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ORIGINAL RESEARCH

Acute Effects on Blood Pressure Following Controlled Exposure to Cookstove Air Pollution in the STOVES Study

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***Background*—**Exposure to air pollution from solid fuel used in residential cookstoves is considered a leading environmental risk factor for disease globally, but evidence for this relationship is largely extrapolated from literature on smoking, secondhand smoke, and ambient fine particulate matter ($PM_{2.5}$).

***Methods and Results*—**We conducted a controlled human-exposure study (STOVES [the Subclinical Tests on Volunteers Exposed to Smoke] Study) to investigate acute responses in blood pressure following exposure to air pollution emissions from cookstove technologies. Forty-eight healthy adults received 2-hour exposures to 5 cookstove treatments (three stone fire, rocket elbow, fan rocket elbow, gasifier, and liquefied petroleum gas), spanning $PM_{2.5}$ concentrations from 10 to 500 $\mu g/m^3$, and a filtered air control (0 $\mu g/m^3$). Thirty minutes after exposure, systolic pressure was lower for the three stone fire treatment (500 $\mu g/m^3$ $PM_{2.5}$) compared with the control (−2.3 mm Hg; 95% CI, −4.5 to −0.1) and suggestively lower for the gasifier (35 $\mu g/m^3$ $PM_{2.5}$; −1.8 mm Hg; 95% CI, −4.0 to 0.4). No differences were observed at 3 hours after exposure; however, at 24 hours after exposure, mean systolic pressure was 2 to 3 mm Hg higher for all treatments compared with control except for the rocket elbow stove. No differences were observed in diastolic pressure for any time point or treatment.

***Conclusions*—**Short-term exposure to air pollution from cookstoves can elicit an increase in systolic pressure within 24 hours. This response occurred across a range of stove types and $PM_{2.5}$ concentrations, raising concern that even low-level exposures to cookstove air pollution may pose adverse cardiovascular effects. **(*J Am Heart Assoc*. 2019;8:e012246. DOI: 10.1161/JAHA.119.012246.)**

Key Words: air pollution • blood pressure • cardiovascular disease risk factors

Nearly 40% of the world's population uses solid fuel for cooking.[1] Exposure to the resulting household air pollution is a major contributor to global disease, particularly in the form of cardiovascular diseases.[2] Although some studies have shown cardiovascular health benefits from improved stove designs that reduce emissions compared with traditional stoves,[3–5] questions remain regarding the level of exposure reduction needed to reduce cardiovascular health burden.[6,7]

The connections between household (ie, cookstove-generated) air pollution and cardiovascular disease risk is extrapolated primarily from research on other pollution sources (ie, active cigarette smoking, secondhand smoke, and ambient air pollution).[8,9] Additional research is needed to explore emissions across a wide variety of cookstove practices, exposure levels, and health responses.

Blood pressure is an established marker of cardiovascular disease risk[10–12] that can increase following acute and chronic exposure to ambient and household air pollution.[4,13–18] Several field studies have investigated relationships between household air pollution exposures and blood pressure,[4,5,17,19–24] with results ranging from null associations to upward of 10-mm Hg increases in systolic pressure

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Accompanying Data S1 and S2, Tables S1–S12, and Figures S1–S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012246

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Clinical Perspective

What Is New?

- We used a novel study design—a controlled human-exposure study—to investigate acute responses in blood pressure following exposure to air pollution emissions from cookstove technologies.
- Results demonstrated that short-term exposures to cookstove-generated air pollution can acutely perturb systolic blood pressure, with a small decrease immediately after exposure and a 2- to 3-mm Hg increase 24 hours after exposure compared with filtered air control.
- Responses were consistent across a range of stove treatment types, with fine particular matter ($PM_{2.5}$) levels ranging from 10 to 500 $\mu g/m^3$.

What Are the Clinical Implications?

- Nearly 40% of the world's population that uses solid fuels for cooking, and replacement of traditional stove technologies with lower particulate matter–emitting technologies has been a major public health focus.
- Our results suggest that household air pollution may be detrimental to cardiovascular health, even at low $PM_{2.5}$ levels.
- Given these findings, public health practitioners and researchers need to carefully consider the intended consequences of cookstove intervention programs and the timelines of exposure-response observations.

for traditional-stove users compared with improved-stove users. Few controlled wood-smoke exposure studies exist,[25–34] and even fewer consider blood pressure; in 2 studies that did measure blood pressure, no effects immediately after exposures were found.[35,36] However, these studies did not include longer follow-up times and observed other acute hemodynamic responses suggestive of vascular impairment and acute autonomic nervous system perturbations.

As part of the STOVES (Subclinical Tests on Volunteers Exposed to Smoke) Study, this work examines changes in blood pressure up to 24 hours following 2-hour exposures to cookstove emissions from 5 stove technologies at characteristic fine particulate matter ($PM_{2.5}$) mass concentrations between 10 and 500 $\mu g/m^3$ and a filtered air control.

Methods

Methods are described briefly herein; more information is in the Supplemental Material. Data from this study are available from the corresponding author upon reasonable request.

Eligibility Criteria and Recruitment Methods

Forty-eight healthy nonsmoking volunteers were recruited through articles in the local and university news, advertisements sent to various university email lists, and word of mouth. Eligibility criteria were based on age, weight, history of disease, drug use, and occupational or incidental pollution exposure, current cardiovascular health status, medication use, and ability to complete the study protocols (full criteria in Data S1). Individuals with occupations that may result in increased air pollution exposures were excluded. Individuals who were interested in participating in the study completed a screening questionnaire and attended an in-person screening examination and physical to ensure they met study criteria (see Data S1). All study protocols were approved by the Colorado State University institutional review board; procedures followed were in accordance with institutional guidelines. All participants provided written informed consent.

Study Design

A sample size of 48 was chosen based on a number of factors including statistical power, budget, reasonability for recruiting in our target population, and maximizing our study design and facility capacities. Each participant underwent six 2-hour exposure treatments over 13 to 16 weeks, with a minimum 2-week period between treatments. We conducted the study in 3 rounds. Within each round, 2 groups of 8 participants alternated weeks until completion of all 6 treatments. Within each week, 4 participants started their study sessions on Mondays and 4 on Wednesdays. Treatment-assignment sequences were determined following a Williams square design, a Latin square crossover that balances treatments and first-order carryover effects.[37] This design is robust for time-invariant factors at the person level (ie, subject effects)—each person receives each treatment—and time-variant factors that might differ across study sessions (eg, ambient conditions, caffeine or alcohol consumption) because the distribution of these variables is expected to be similar across all treatments when data are balanced.[38,39] Participants who missed a scheduled study session could make up the missed treatment at the end of their sequence. Participants were not told which treatment they were assigned to on each visit.

Study Session Protocol

The timeline of a study session is illustrated in Figure 1. Participants were instructed to abstain from medications, nutritional supplements, and vitamins starting 72 hours before each study day and from caffeine, alcohol, strenuous exercise, and smoke exposures (eg, campfires/wood stoves, secondhand smoke) starting 24 hours before and continuing

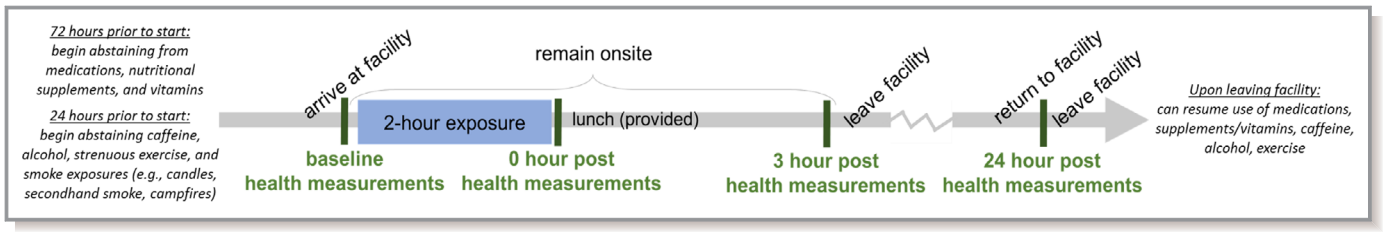

Figure 1. Timeline of a study session. Participants arrived at the facility at the same time on each of their assigned study session dates (between 7:30 and 9 AM) and completed the same protocols at each session according to the timeline shown. Participants completed sessions with a minimum of 10 days (typically 2–3 weeks) between sessions.

through the 24-hour follow-up period. Participants were also asked to avoid high-fat and high-cholesterol foods on study days. Surveys were administered to determine compliance with these protocols (see Health and Additional Measurements). There were no restrictions on lifestyle, food, or activity between study sessions aside from maintaining compliance with the eligibility criteria.

Participants arrived at the facility at the same time and followed the same protocols and schedule each study session. Participants were asked about current or recent illnesses at the start of each session, and an on-site physician approved participation each day. Baseline health measurements were conducted on arrival (see Health and Additional Measurements). Participants then spent 2 hours in the exposure chamber receiving the treatment; the physician remained on-site during exposures and confirmed that participants did not have any acute concerns on exiting the chamber; the physician was also available on call for 24 hours after the end of the exposure period. Additional rounds of health measurements were conducted starting immediately after exposure and 3 hours after exposure. Participants remained on-site between measurements, and lunch was provided (low fat or low cholesterol; same each session). Participants returned for a final round of health measurements 24 hours after the end of the exposure treatment.

Treatments and Administration

The exposure chamber consisted of a main exposure room (2.7 m height×3.5 m width×2.8 m length) and an airlock/anteroom. Up to 4 participants could be in the chamber at the same time. Participants' blood pressure, heart rate, and oxygen saturation levels were recorded by a registered nurse every 15 minutes during the exposure, for safety purposes.

Treatments consisted of a high-efficiency particulate air–filtered control and pollution generated from 5 different cookstoves, chosen to represent commonly used technologies and span the International Standard Organization's (ISO's) cookstove performance tiers.[40] A target $PM_{2.5}$ exposure concentration was chosen for each stove. Setting target concentrations with a narrow tolerance for each stove allowed for increased statistical power to resolve between-stove differences while abiding by protocols for participant safety and informed consent. Target concentrations were aligned with the ISO performance tiers and values realistically expected for the stove when used in the real world[20,41–43] while considering the feasibility of achieving the level with each stove within our facility and maintaining distinct distributions of exposures for each treatment. Cookstoves were a liquefied petroleum gas (LPG) stove (10 $\mu g/m^3$), a gasifier (35 $\mu g/m^3$), a forced-draft (fan-powered) rocket elbow ("fan rocket," 100 $\mu g/m^3$), a natural-draft rocket elbow ("rocket elbow," 250 $\mu g/m^3$), and a three stone fire (500 $\mu g/m^3$). Pollution was generated within a total-capture fume hood, diluted with high-efficiency particulate air–filtered laboratory air, and then drawn into the exposure chamber. Carbon monoxide, $PM_{2.5}$, oxygen, temperature, and humidity in the chamber were monitored in real time; a dynamic control system (LabVIEW, v15.0 32-bit; National Instruments) automated the real-time $PM_{2.5}$ averaging and dilution process. Real-time $PM_{2.5}$ was measured using a DustTrak DRX (model 8533; TSI Inc).

Additional treatment emissions characterization was conducted at the end of the study. The facility was operated for 2 hours under the same conditions as during human exposures but without participants present, on at least 2 occasions per treatment. Air was sampled from the facility for measurement of $PM_{2.5}$ mass, particle-number size distributions (10 to 500 nm), organic and elemental carbon (EC) concentrations, nitrogen oxide, nitrogen dioxide, volatile organic compounds, and carbonyls (see Data S1).

Health and Additional Measurements

Brachial blood pressure was measured 4 times per session: before exposure, immediately after exposure, 3 hours after exposure, and 24 hours after exposure. Measurements were performed on the left upper arm with participants in a supine position after a minimum 10-minute rest period using an automated oscillatory monitor (SphygmoCor XCEL; AtCor

Medical Pty Ltd). Three readings were taken 1 minute apart; the average of the last 2 measurements was used in the analysis.[44]

Questionnaires were administered to assess compliance with protocols and other factors across study sessions, such as the participant's mode of commute to our facility and incidental smoke exposures. Hourly ambient data for the 24 hours before and throughout each study session were downloaded from the US Environmental Protection Agency's Air Quality Data air pollution index and a local weather station.[45,46]

Statistical Analysis

Data processing and statistical analyses were performed in R (v3.3.1; R Foundation for Statistical Computing).

Summary statistics (mean±SD, range) were calculated for anthropometric values for the total population and by sex. Each participant's mean $PM_{2.5}$ and CO exposures were determined by averaging the 1-second data over the 2-hour exposure window; the population standard deviation and range were determined from the 2-hour averages. Additional emissions-characterization measurements (collected after the study ended) were averaged across each treatment.

Linear mixed-effect models were employed (using the lme4 package[47]) to estimate the difference between blood pressure at each post-exposure time point for each stove treatment compared with the control. Separate models were run for each time point (immediate, 3-hour, 24-hour) and for each blood pressure metric (systolic, diastolic). Model assumptions were evaluated by examining the normality of the model's residuals, linearity of the fitted models, and equality of the error variance. We also identified potential outliers in the data and examined the impact of the outliers on model fit.

The primary models contained a fixed effect of categorical treatment, a random person intercept to account for nonindependence across repeated measures within the crossover design, a random effect for date to account for within-day correlation for individuals who received treatments on the same day, and the pre-exposure blood pressure value to account for differences in individuals' starting blood pressure across treatments or study sessions (which captures information similar to a pre-/post-exposure change model but is more efficient and easier to interpret).[48,49] By using stove treatment type in the model, we capture the combined effect of all the emissions from the stove (eg, particle and gases) on blood pressure compared with control. The study design eliminates the need to control for individual-level confounders (eg, age, sex), as each person participates in each treatment, and external confounders that might vary across study days (eg, ambient conditions, caffeine or alcohol consumption), as each person participates in each treatment and treatments are balanced across time.[38,39] Descriptive statistics and bivariate analyses were conducted to confirm that associations between these covariates and the treatment groups did not occur by chance or because of imbalances caused by missing data.

Additional models were evaluated as alternatives to the main model. We developed a mixed-effect model that considered more structured study design parameters relevant to our Williams square, including assigned sequence group and day of the week (Monday versus Wednesday). Only data that were collected within the intended sequence (ie, not including makeup sessions) were used in this model. We also ran the same model as the primary model but (1) excluding data collected outside of the intended sequence and (2) excluding data from study sessions in which the exposure mean was outside of a narrowed range around the target value.

Results

Participants

The 48 participants (26 male, 22 female) ranged from 21 to 36 years old (mean±SD: 27.5±3.6 years), were within the normal or low-overweight body mass index (kg/m^2) categories (mean±SD: 23.4±2.2), and on average had nonhypertensive baseline blood pressure (mean±SD for systolic/diastolic: 116±9/69±6 mm Hg; Table 1). Values were comparable between men and women. Participants predominantly identified as non-Hispanic white (42/48; 88%). Reported use of alcohol, caffeine, and medication were low throughout the study; bivariate analyses indicated no meaningful associations between these or other potentially confounding covariates (eg, ambient $PM_{2.5}$ and CO) and the various treatments (see Data S2 and Tables S2–S11).

The total missing data rate was 6% (see Data S2). Of the 48 participants, 22 (46%) completed the study in the intended, assigned order with no missed treatments. Age, sex, and body mass index were comparable between participants who missed sessions and those who did not (see Data S2). Using makeup dates at the end of a study round to complete missed treatments, 79% of participants (38/48) contributed data relevant to all 6 treatments, and 94% (45/48) had data for at least 5 treatments.

Exposure Conditions

The means and ranges of individual 2-hour exposure averages within each treatment are provided in Table 2. The means of participants' averaged $PM_{2.5}$ mass exposure concentrations were within 10% of the target for the fan rocket, rocket elbow, and three stone fire treatments (+5, +4, and −37 $\mu g/m^3$,

Table 1. Description of Study Participants

Variable	All (n=48)	Female (n=22)	Male (n=26)
BMI, kg/m^2	23.4 [2.2], 19.4, 28.7	23.5 [2.6], 19.7, 28.7	23.3 [2.0], 19.4, 26.0
Age, y	27.5 [3.6], 20.5, 36.1	27.5 [3.4], 22.8, 34.0	27.4 [3.9], 20.5, 36.1
Baseline SBP, mm Hg	116 [9], 99, 135	113 [9], 100, 135	118 [8], 99, 135
Baseline DBP, mm Hg	69 [6], 59, 86	69 [7], 60, 86	69 [5], 59, 80
Participants with data for all 6 treatments†	79	82	77
Participants with data for at least 5 treatments†	94	100	88

Data are shown as mean [SD],* minimum, maximum, or percentage. BMI indicates body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
*Mean calculated as the population mean of each individuals' average baseline health measurement across their completed study sessions.
†Participant was counted if he or she had data for baseline measurement and at least 1 post-exposure measurement.

respectively), 20% for the LPG treatment (+2 μg/m^3), and 30% for the gasifier treatment (+16 μg/m^3). The mean of participants' averaged CO exposures per treatment type generally increased with increasing $PM_{2.5}$, ranging from 2 ppm for the control up to 9 ppm for the three stone fire.

Additional pollutant measurements conducted after the end of the study were used to characterize particle properties and quantify the coemitted gases in the cookstove smoke compared with the control filtered air. Nitrogen oxide concentrations were elevated for all stove treatments compared with the control, with the largest differences for the fan rocket and rocket elbow stoves (24 ppb each, compared with 1 ppb for the control, 4 ppb for LPG and three stone fire, and 2 ppb for gasifier). Nitrogen dioxide levels were similar for all treatments, including the control (range: 8–12 ppb). Gaseous carbonyls were measured in all treatments including the control, with the highest levels for LPG, rocket elbow, and three stone fire (197, 194, and 293 μg/m^3, respectively, versus 107, 128, and 131 μg/m^3 for control, gasifier, and fan rocket). EC concentration was notably higher for the rocket elbow stove (94 μg/m^3; EC:$PM_{2.5}$ ratio: 0.7) compared with the other treatments (0, 3, 29, 38, and 30 for control, LPG, gasifier, fan rocket, and three stone fire; EC:$PM_{2.5}$ ratios of 0.1–0.5). Although total particle number generally increased in a $PM_{2.5}$ mass-dependent manner, ultrafine particle number fraction was considerably higher for the LPG treatment than all others (<95% of particles were <100 nm versus 60–70% for all others). Within the smallest measured size, 10 to 30 nm, the absolute particle number for the LPG treatment was ≈4 times higher than for the gasifier and three stone fire (which were similar), 65% higher than for the rocket elbow, and 25% higher than for the fan rocket. Additional detail is provided in Data S2, Table S1, and Figure S1.

Differences in Blood Pressure for Stove Treatments Compared With Control

Blood pressure measurements occurred on average 30 minutes (SD: 4.2 minutes) after exposure for the immediate time point, 3 hours and 26 minutes (SD: 4.8 minutes) for the 3-hour time point, and 24 hours and 13 minutes (SD: 30 minutes) for the 24-hour time point (see Data S2). Mean blood pressure across all participants, treatments, and time points was nonhypertensive (average: 115.7/68.9 mm Hg), although some individual measurements were within a hypertensive range (measurements with systolic pressure ≥130 mm Hg: 9%; measurements with diastolic pressure ≥80 mm Hg: 8%).

Table 2. Distributions of the Individual Mean 2-Hour Pollutant Exposures Measured During Treatments

Treatment*	Fuel	Participants Completing Treatment (n)	$PM_{2.5}$ (μg/m^3)		CO (ppm)	
			Mean [SD]†	Min, Max Individual Exposure†	Mean [SD]†	Min, Max Individual Exposure†
Control	None	47	1 [2]	−1‡, 9	2 [2]	1, 10
LPG	Propane	44	8 [3]	3, 13	3 [1]	1, 6
Gasifier	Wood chips	44	46 [9]	30, 76	5 [3]	1, 14
Fan rocket	Wood sticks	44	95 [9]	77, 111	8 [2]	5, 12
Rocket elbow	Wood sticks	45	254 [9]	236, 276	6 [2]	3, 11
Three stone fire	Wood sticks	47	463 [41]	367, 531	9 [4]	4, 20

LPG indicates liquefied petroleum gas; max, maximum; min, minimum; $PM_{2.5}$, fine particular matter.
*Target $PM_{2.5}$ levels for each treatment were high-efficiency particulate air-filtered air (0 μg/m^3), LPG (10 μg/m^3), gasifier (35 μg/m^3), fan rocket (100 μg/m^3), rocket elbow (250 μg/m^3), and three stone fire (500 μg/m^3). CO did not have a target level and was not controlled but rather varied naturally.
†Measured pollutant mean is of the participants' 2-h average values, calculated by determining the 2-h average of the 1-s exposure data for each participant and then averaging across all participants for each treatment. Min and max individual values are the lowest and highest 2-h average value measured for a single participant.
‡Negative values are a result of a DustTrak calibration artifact.

Average pre-exposure blood pressure varied by treatment type (highest: three stone fire, 117.0/70.2 mm Hg; lowest: fan rocket, 115.0/68.2 mm Hg).

Effect estimates and 95% CIs for the difference in blood pressure after exposure for each stove treatment compared to the control from the main model are presented in Table 3 and Figure 2. Alternative model results were consistent with the main model (see Data S2, Table S12, and Figures S2–S5).

At the immediate post-exposure measurement, systolic pressure was significantly lower compared with the filtered air control for the three stone fire treatment (500 μg/m^3 $PM_{2.5}$: −2.3 mm Hg; 95% CI, −4.5 to −0.1) and suggestively lower for the gasifier (35 μg/m^3 $PM_{2.5}$: −1.8; 95% CI, −4.0 to 0.4). Other treatments were not meaningfully different from the control at the immediate post-exposure time point.

No significant differences were observed for systolic pressure between the control and treatments at 3 hours post-exposure. However, effect estimates were ≈2 mm Hg lower than the control for the fan rocket (100 μg/m^3 $PM_{2.5}$: −1.76 mm Hg; 95% CI, −4.02 to 0.50) and three stone fire (500 μg/m^3 $PM_{2.5}$: −2.05; 95% CI, −4. to 0.15) treatments. Effect estimates were ≈1 mm Hg higher than the control for the LPG (10 μg/m^3 $PM_{2.5}$: 1.10 mm Hg; 95% CI, −1.1 to 3.33) and gasifier (35 μg/m^3 $PM_{2.5}$: 0.99 mm Hg; 95% CI, −1.2 to 3.23) treatments.

At 24 hours post-exposure, systolic pressure was significantly higher than the control by 2 to 3 mm Hg for all treatments except the rocket elbow. These large significant effects followed a consistent pattern across stoves, with effect estimates ranging from 2.3 to 3.1 mm Hg and 95% CIs ranging from 0.1 to 5.3 mm Hg for the LPG, gasifier, fan rocket, and three stone fire treatments (LPG: 3.11 mm Hg [95% CI, 0.65–5.27]; gasifier: 2.3 mm Hg [95% CI, 0.11–4.48]; fan rocket: 2.54 mm Hg [95% CI, 0.39–4.70]; three stone fire: 2.41 mm Hg [95% CI, 0.28–4.53]).

Differences were consistent with the null for diastolic pressure at every time point for all stove treatments compared with the control except for the rocket elbow treatment at 24 hours after exposure, which was suggestive of lower diastolic pressure compared with the control.

Discussion

Exposure to household air pollution is a leading contributor to disease worldwide, yet there are many gaps in our understanding of how different stoves and exposure levels contribute to health effects. We observed evidence that short-term exposures to cookstove emissions resulted in a 2- to 3-mm Hg increase in systolic pressure compared with filtered air control at 24 hours after exposure. Conversely, 30 minutes after exposure we observed small nonsignificant decreases in systolic pressure compared with control that generally returned to no difference 3 hours after exposure. These differences were seen across stove types at $PM_{2.5}$ levels from 10 to 500 μg/m^3 and did not appear to follow an exposure-response pattern that corresponded with increasing

Table 3. Mean Difference in Blood Pressure for Stove Treatments Compared With Control at Each Measurement Time

Treatment	Baseline*Value mmHg [Mean (SD)]	Effect Estimate (95% CI) [mm Hg Difference Compared With Control Treatment]†		
		Immediately After Exposure	3 h After Exposure	24 h After Exposure
Systolic pressure				
LPG	116.5 (10.7)	−0.2 (−2.5 to 2.0)	1.1 (−1.1 to 3.3)	3.1 (1.0–5.3)
Gasifier	115.7 (10.8)	−1.8 (−4.0 to 0.4)	1.0 (−1.2 to 3.2)	2.3 (0.1–4.5)
Fan rocket	115.0 (9.2)	−0.4 (−2.7 to 1.8)	−1.8 (−4.0 to 0.5)	2.5 (0.4–4.7)
Rocket elbow	115.6 (9.7)	−0.58 (−2.8 to 1.6)	−0.5 (−2.7 to 1.7)	−0.1 (−2.2 to 2.1)
Three stone fire	117.0 (11.3)	−2.3 (−4.5 to −0.1)	−2.1 (−4.3 to 0.2)	2.4 (0.3–4.5)
Diastolic pressure				
LPG	69.2 (6.7)	−0.7 (−2.2 to 0.8)	−0.0 (−1.7 to 1.7)	0.3 (−1.6 to 2.2)
Gasifier	69.1 (6.9)	−0.8 (−2.2 to 0.7)	0.25 (−1.5 to 2.0)	−0.4 (−2.3 to 1.5)
Fan rocket	68.2 (7.3)	−0.1 (−1.6 to 1.4)	−0.4 (−2.2 to 1.3)	−0.1 (−1.9 to 1.8)
Rocket elbow	69.1 (7.3)	0.4 (−1.1 to 1.8)	0.2 (−1.5 to 1.9)	−1.7 (−3.6 to 0.2)
Three stone fire	70.2 (7.6)	−0.9 (−2.3 to 0.60)	−0.8 (−2.5 to 0.9)	0.8 (−1.0 to 2.7)

LPG indicates liquefied petroleum gas.
*Control value at baseline: systolic: 115.2 (9.6) mm Hg; diastolic: 68.6 (6.6).
†All estimates are adjusted for baseline (pre-exposure) blood pressure.

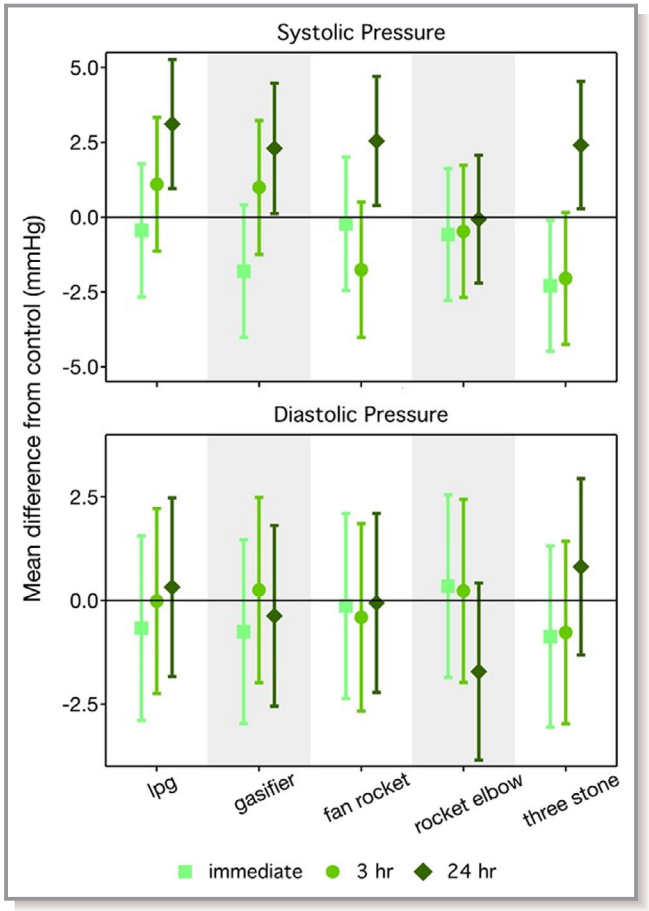

Figure 2. Effect estimates and confidence intervals for difference in blood pressure for stove treatment compared with control, by stove type and post-exposure time point. Top: Systolic pressure. Bottom: Diastolic pressure. LPG indicates liquefied petroleum gas.

$PM_{2.5}$ or CO concentrations. Results for diastolic pressure were generally consistent with the null hypothesis for all times and stove treatments.

Particulate matter air pollution is hypothesized to elicit vascular dysfunction through a variety of mechanistic pathways including activation of the autonomic nervous system and increased parasympathetic responses, proinflammatory responses leading to oxidative stress and inflammation, and direct interaction of particles with molecules in blood circulation that regulate endothelial function and cell signaling.[13] Recent evidence supports an adrenal stress response (eg, increased glucocorticoids due to hypothalamic–pituitary–adrenal axis activation) may also be involved in particulate matter–induced blood pressure elevations.[50] Our observed responses suggest that short-term exposure to air pollution from most cookstoves (regardless of $PM_{2.5}$ levels) produced a delayed increase in systolic pressure that was observable within 24 hours. As reviewed elsewhere,[18] a delayed increase is suggestive of biological pathways with slower onset but more persistent actions. This could include hypothalamic–pituitary–adrenal axis activation and/or vasomotor dysfunction induced by slower proinflammatory (eg, cytokine-mediated) mechanisms. Further work to investigate circulating inflammatory or hypothalamic–pituitary–adrenal axis markers would help confirm this hypothesis. The lack of acute increase in blood pressure does not support autonomic nervous system activation.[14] There are multiple mechanisms through which air pollution exposures could result in biological changes that affect systolic pressure more than diastolic pressure; for example, if air pollution exposure causes increased arterial stiffness (as suggested by some work[51]), this would favor greater changes in systolic pressure. More work is needed to elucidate these pathways.

The post-exposure times for health measurements were chosen because of a combination of logistical considerations within our study protocols and because they represent potentially key response times within the mechanistic pathway for cardiovascular effects from air pollution.[14] However, it is possible that the timing of our measurements (starting 30 minutes after the exposure ended) missed an immediate blood pressure increase during particle inhalation. Prior controlled inhalation studies with diesel particles and concentrated $PM_{2.5}$ have shown that blood pressure can increase by $\geq$2 mm Hg immediately (within minutes) during short-duration exposures in the 100- to 200-$\mu g/m^3$ $PM_{2.5}$ range but does not stay elevated after particle inhalation ceases (subsiding within a few minutes to hours).[16,18,52–55] Only 1 of the identified studies maintained follow-up through 24 hours; no effect was observed at this time.[52] If this acute autonomic blood pressure elevation occurred in our study, we may not have observed it given our design. Perturbations that may have occurred during the exposure window, which are likely to be through an immediate autonomic nervous system activation pathway, might have subsided by the time post-exposure measurements were conducted. Future studies that assess the blood pressure responses concomitant with exposure can help clarify this issue. Alternatively, if small changes in systolic pressure occurred at the immediate or 3-hour time point, our study may not have been sufficiently powered to detect them. Our study may have been underpowered to detect effects in diastolic pressure at any time point because diastolic pressure is measured with less accuracy than systolic pressure, is more variable, and has a smaller absolute value and range.

Previous work suggests that the adverse cardiovascular effects of diesel exhaust exposure are entirely attributed to the particulate phase.[56] It is possible that the complex mix of gaseous and particle pollutants in cookstove combustion results in competing vasoconstricting and vasodilatory effects that manifest differently across different stove types. For example, coemitted NO may have elicited a

vasodilation response that obfuscated an immediate $PM_{2.5}$-induced blood pressure elevation. However, we do not have sufficient data on the multipollutant exposures to further support this hypothesis. Further work to assess blood pressure changes in studies that remove gaseous coexposures, leaving only cookstove particles, could help clarify these speculations.

Moreover, it is possible that we did not observe immediate effects on blood pressure (as is seen in ambient studies) because compositional differences in LPG and wood combustion emissions compared with ambient pollution result in different responses. The pollutant characterization tests conducted after the study ended demonstrated differences in particle composition (eg, EC and ultrafine levels) across stove types, suggesting that acute responses to air pollution of similar $PM_{2.5}$ levels but from different sources may not be comparable. Few controlled wood-smoke exposure studies exist and none use advanced cookstoves or nonbiomass LPG fuel; investigation of blood pressure in these studies is further limited. However, results generally align with our findings. Unosson et al[35] found no changes in systolic or diastolic pressure during the 1 hour after a 3-hour exposure to birch wood smoke (300 $\mu g/m^3$ $PM_{2.5}$) generated by a Nordic chimney stove compared with filtered air exposure. Evans et al[36] reported no immediate effects on systolic pressure following 20-minute exposure sessions to environmental tobacco smoke, cooking oil fumes, and cedar wood smoke (peak concentration target 350 $\mu g/m^3$, generated by open burning) compared with a water vapor control. Neither study included a delayed follow-up measure (eg, 24 hours). Hunter et al[57] found no changes in blood pressure among firefighters during a 1-hour controlled exposure to birch wood smoke generated by a Nordic chimney stove (1000 $\mu g/m^3$) or at follow-up 6 and 24 hours after exposure ended; however, this population may be less susceptible to acute impacts of smoke than a general population.

We did not observe an acute exposure-response relationship between $PM_{2.5}$ mass and blood pressure. A possible explanation for these findings is that other smoke constituents (besides $PM_{2.5}$ mass) may be responsible for eliciting some or all of the observed blood pressure responses. No single pollutant provides an obvious explanation for the similar systolic pressure responses across most of the stove treatments or the null response for the rocket elbow treatment compared with the control at 24 hours post-exposure. Alternatively, an exposure-response curve for cookstove smoke and blood pressure may not exist on the timescale studied (2-hour exposures, 24-hour follow-up). Previous work suggesting supralinear exposure-response curves for air pollution are for different cardiovascular end points (eg, ischemic heart disease, cardiovascular mortality) and long-term exposures;[9,58] although some limited cross-sectional analyses of in-field cookstove exposures and blood pressure suggest that a nonlinear relationship exists for individuals with chronic exposures.[20,51] Studies of acute cigarette exposures suggest that changes in subclinical cardiovascular function may occur at similar levels for active and passive smoking.[59,60] Our results suggest an acute threshold effect may occur for cookstove air pollution, with similar responses in blood pressure following exposure regardless of $PM_{2.5}$ concentration levels or source (eg, LPG versus wood). It is unclear how the results of our study might translate under long-term-exposure scenarios.

Participants were young, predominantly white, healthy individuals with limited air pollution exposures in their daily lives; therefore, the generalizability of results to cookstove users globally may be limited. This population was feasible to study in this context in terms of participant safety and allowed us to minimize confounding or interactions by age, comorbid disease status, or other pollution exposures. Our study has strong internal validity accomplished by the controlled exposure design, and this strengthens the study's ability to balance data gaps of potentially more generalizable but less internally valid observational studies.

Our study expands on previous air pollution controlled exposure studies by incorporating more exposure levels, allowing for confidence in statistically suggestive trends; including more participants for greater power; and generating treatment exposures from multiple cookstove types. The Williams square crossover design and restrictive study protocols allowed for within-person comparisons and eliminated many potential confounders, resulting in efficient analyses comparing more stove types and exposure levels than observational designs.

We demonstrated that short-term exposures to cookstove-generated air pollution can acutely perturb systolic pressure, with a small decrease immediately after exposure and a 2- to 3-mm Hg increase 24 hours after exposure compared with filtered air control. Responses were consistent across a range of stove treatment types, with $PM_{2.5}$ levels ranging from 10 to 500 $\mu g/m^3$, which suggests that household air pollution may be detrimental to cardiovascular health, even at low $PM_{2.5}$ levels. Given these findings, public health practitioners and researchers need to carefully consider the intended consequences of cookstove intervention programs and the timelines of exposure-response observations. Further work is needed to better characterize the multipollutant exposures from household air pollution and aid in understanding the relationship to blood pressure across a range of smoke exposure compositions. Researchers must also carefully consider how acute exposure-response relationships seen in controlled exposure studies

translate to real-world, chronic exposures because different exposure and response timelines and populations may affect results.

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None.

References

1. Bonjour S, Adair-Rohani H, Wolf J, Bruce NG, Mehta S, Pruss-Ustun A, Lahiff M, Rehfuess EA, Mishra V, Smith KR. Solid fuel use for household cooking: country and regional estimates for 1980–2010. *Environ Health Perspect*. 2013;121:784–790.
2. Stanaway JD; GBD 2017 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1923–1994.
3. McCracken J, Smith KR, Stone P, Diaz A, Arana B, Schwartz J. Intervention to lower household woodsmoke exposure in Guatemala reduces ST-segment depression on electrocardiograms. *Environ Health Perspect*. 2011;119:1562–1568.
4. McCracken JP, Smith KR, Diaz A, Mittleman MA, Schwartz J. Chimney stove intervention to reduce long-term wood smoke exposure lowers blood pressure among Guatemalan women. *Environ Health Perspect*. 2007;115:996–1001.
5. Dutta A, Brito K, Khramstova G, Mueller A, Chinthala S, Alexander D, Adu D, Ibigbami T, Olamijulo J, Odetunde A, Adigun K, Pruitt L, Olopade O, Ojengbede O, Rana S, Olopade CO. Household air pollution and angiogenic factors in pregnant Nigerian women: a randomized controlled ethanol cookstove intervention. *Sci Total Environ*. 2017;599–600:2175–2181.
6. Smith KR, Peel JL. Mind the gap. *Environ Health Perspect*. 2010;118:1643–1645.
7. Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam K-BH, Mortimer K, Asante KP, Balakrishnan K, Balmes J, Bar-Zeev N, Bates MN, Breysse PN, Buist S, Chen Z, Havens D, Jack D, Jindal S, Kan H, Mehta S, Moschovis P, Naeher L, Patel A, Perez-Padilla R, Pope D, Rylance J, Semple S, Martin WJ. Respiratory risks from household air pollution in low and middle income countries. *Lancet Respir Med*. 2014;2:823–860.
8. Smith KR, Bruce N, Balakrishnan K, Adair-Rohani H, Balmes J, Chafe Z, Dherani M, Hosgood HD, Mehta S, Pope D, Rehfuess E. Millions dead: how do we know and what does it mean? Methods used in the comparative risk assessment of household air pollution. *Annu Rev Public Health*. 2014;35:185–206.
9. Burnett RT, Pope CA III, Ezzati M, Olives C, Lim SS, Mehta S, Shin HH, Singh G, Hubbell B, Brauer M, Anderson HR, Smith KR, Balmes JR, Bruce NG, Kan H, Laden F, Pruss-Ustun A, Turner MC, Gapstur SM, Diver WR, Cohen A. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. *Environ Health Perspect*. 2014;122:397–403.
10. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345:1291–1297.
11. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
12. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–1535.
13. Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.
14. Langrish J, Bosson J, Unosson J, Muala A, Newby D, Mills N, Blomberg A, Sandström T. Cardiovascular effects of particulate air pollution exposure: time course and underlying mechanisms. *J Intern Med*. 2012;272:224–239.
15. Fuks KB, Weinmayr G, Foraster M, Dratva J, Hampel R, Houthuijs D, Oftedal B, Oudin A, Panasevich S, Penell J, Sommar JN, Sorensen M, Tiittanen P, Wolf K, Xun WW, Aguilera I, Basagana X, Beelen R, Bots ML, Brunekreef B, Bueno-de-Mesquita HB, Caracciolo B, Cirach M, de Faire U, de Nazelle A, Eeftens M, Elosua R, Erbel R, Forsberg B, Fratiglioni L, Gaspoz JM, Hilding A, Jula A, Korek M, Kramer U, Kunzli N, Lanki T, Leander K, Magnusson PK, Marrugat J, Nieuwenhuijsen MJ, Ostenson CG, Pedersen NL, Pershagen G, Phuleria HC, Probst-Hensch NM, Raaschou-Nielsen O, Schaffner E, Schikowski T, Schindler C, Schwarze PE, Sogaard AJ, Sugiri D, Swart WJ, Tsai MY, Turunen AW, Vineis P, Peters A, Hoffmann B. Arterial blood pressure and long-term exposure to traffic-related air pollution: an analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Environ Health Perspect*. 2014;122:896–905.
16. Urch B, Silverman F, Corey P, Brook JR, Lukic KZ, Rajagopalan S, Brook RD. Acute blood pressure responses in healthy adults during controlled air pollution exposures. *Environ Health Perspect*. 2005;113:1052–1055.
17. Norris C, Goldberg MS, Marshall JD, Valois MF, Pradeep T, Narayanswamy M, Jain G, Sethuraman K, Baumgartner J. A panel study of the acute effects of personal exposure to household air pollution on ambulatory blood pressure in rural Indian women. *Environ Res*. 2016;147:331–342.
18. Brook RD, Newby DE, Rajagopalan S. Air pollution and cardiometabolic disease: an update and call for clinical trials. *Am J Hypertens*. 2017;31:1–10.
19. Alexander D, Larson T, Bolton S, Vedal S. Systolic blood pressure changes in indigenous Bolivian women associated with an improved cookstove intervention. *Air Qual Atmos Health*. 2015;8:47–53.
20. Baumgartner J, Schauer JJ, Ezzati M, Lu L, Cheng C, Patz JA, Bautista LE. Indoor air pollution and blood pressure in adult women living in rural China. *Environ Health Perspect*. 2011;119:1390–1395.
21. Clark ML, Bachand AM, Heiderscheidt JM, Yoder SA, Luna B, Volckens J, Koehler KA, Conway S, Reynolds SJ, Peel JL. Impact of a cleaner-burning cookstove intervention on blood pressure in Nicaraguan women. *Indoor Air*. 2013;23:105–114.
22. Clark ML, Bazemore H, Reynolds SJ, Heiderscheidt JM, Conway S, Bachand AM, Volckens J, Peel JL. A baseline evaluation of traditional cook stove smoke exposures and indicators of cardiovascular and respiratory health among Nicaraguan women. *Int J Occup Environ Health*. 2011;17:113–121.
23. Burroughs Pena M, Romero KM, Velazquez EJ, Davila-Roman VG, Gilman RH, Wise RA, Miranda JJ, Checkley W. Relationship between daily exposure to biomass fuel smoke and blood pressure in high-altitude Peru. *Hypertension*. 2015;65:1134–1140.
24. Neupane M, Basnyat B, Fischer R, Froeschl G, Wolbers M, Rehfuess EA. Sustained use of biogas fuel and blood pressure among women in rural Nepal. *Environ Res*. 2015;136:343–351.
25. Ferguson MD, Semmens EO, Dumke C, Quindry JC, Ward TJ. Measured pulmonary and systemic markers of inflammation and oxidative stress following wildland firefighter simulations. *J Occup Environ Med*. 2016;58:407–413.
26. Ferguson MD, Semmens EO, Weiler E, Domitrovich J, French M, Migliaccio C, Palmer C, Dumke C, Ward T. Lung function measures following simulated wildland firefighter exposures. *J Occup Environ Hyg*. 2017;14:739–748.
27. Peters B, Ballmann C, Quindry T, Zehner EG, McCroskey J, Ferguson M, Ward T, Dumke C, Quindry JC. Experimental woodsmoke exposure during exercise and blood oxidative stress. *J Occup Environ Med*. 2018;60:1073–1081.
28. Riddervold IS, Bonlokke JH, Molhave L, Massling A, Jensen B, Gronborg TK, Bossi R, Forchhammer L, Kjaergaard SK, Sigsgaard T. Wood smoke in a controlled exposure experiment with human volunteers. *Inhal Toxicol*. 2011;23:277–288.
29. Riddervold IS, Bonlokke JH, Olin AC, Gronborg TK, Schlunssen V, Skogstrand K, Hougaard D, Massling A, Sigsgaard T. Effects of wood smoke particles from wood-burning stoves on the respiratory health of atopic humans. *Part Fibre Toxicol*. 2012;9:12.
30. Forchhammer L, Moller P, Riddervold IS, Bonlokke J, Massling A, Sigsgaard T, Loft S. Controlled human wood smoke exposure: oxidative stress, inflammation and microvascular function. *Part Fibre Toxicol*. 2012;9:7.

31. Bonlokke JH, Riddervold IS, Gronborg TK, Skogstrand K, Hougaard DM, Barregard L, Sigsgaard T. Systemic effects of wood smoke in a short-term experimental exposure study of atopic volunteers. *J Occup Environ Med*. 2014;56:177–183.
32. Ghio AJ, Soukup JM, Case M, Dailey LA, Richards J, Berntsen J, Devlin RB, Stone S, Rappold A. Exposure to wood smoke particles produces inflammation in healthy volunteers. *Occup Environ Med*. 2012;69:170–175.
33. Stockfelt L, Sallsten G, Olin AC, Almerud P, Samuelsson L, Johannesson S, Molnar P, Strandberg B, Almstrand AC, Bergemalm-Rynell K, Barregard L. Effects on airways of short-term exposure to two kinds of wood smoke in a chamber study of healthy humans. *Inhal Toxicol*. 2012;24:47–59.
34. Stockfelt L, Sallsten G, Almerud P, Basu S, Barregard L. Short-term chamber exposure to low doses of two kinds of wood smoke does not induce systemic inflammation, coagulation or oxidative stress in healthy humans. *Inhal Toxicol*. 2013;25:417–425.
35. Unosson J, Blomberg A, Sandström T, Muala A, Boman C, Nyström R, Westerholm R, Mills NL, Newby DE, Langrish JP. Exposure to wood smoke increases arterial stiffness and decreases heart rate variability in humans. *Part Fibre Toxicol*. 2013;10:20.
36. Evans JM, Jenkins RA, Ilgner RH, Knapp CF, Zhang Q, Patwardhan AR. Acute cardiovascular autonomic responses to inhaled particulates. *Eur J Appl Physiol*. 2015;115:257–268.
37. Williams EJ. Experimental designs balanced for the estimation of residual effects of treatments. *Aust J Sci Res Ser A*. 1949;2:149–168.
38. Kenward MG. Crossover designs. In: Wright JD, ed. *International Encyclopedia of the Social & Behavioral Sciences*. 2nd ed. Oxford, England: Elsevier; 2015:349–353.
39. Jones B, Kenward M. *Design and Analysis of Cross-Over Trials*. 3rd ed. Boca Raton, FL: CRC Press; 2014.
40. ISO (International Organization for Standardization). Clean cookstoves and clean cooking solutions—harmonized laboratory test protocols—Part 3: voluntary performance targets for cookstoves based on laboratory testing. 2018.
41. Clark ML, Peel JL, Balakrishnan K, Breysse PN, Chillrud SN, Naeher LP, Rodes CE, Vette AF, Balbus JM. Health and household air pollution from solid fuel use: the need for improved exposure assessment. *Environ Health Perspect*. 2013;121:1120–1128.
42. Balakrishnan K, Mehta S, Ghosh S, Johnson M, Brauer M, Zhang J, Naeher L, Smith KR. Who indoor air quality guidelines: household fuel combustion—review 5: population levels of household air pollution and exposures. 2014.
43. Pope D, Bruce N, Dherani M, Jagoe K, Rehfuess E. Real-life effectiveness of 'improved' stoves and clean fuels in reducing $PM_{2.5}$ and CO: systematic review and meta-analysis. *Environ Int*. 2017;101:7–18.
44. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115.
45. U.S. Environmental Protection Agency. Air quality data API. Available at: https://aqs.epa.gov/api. Accessed 2019 4, June.
46. Colorado State University. Atmospheric Science Department's Christman Field Weather Station data. Available at: https://www.atmos.colostate.edu/fccwx/fccwx_data_form.php. Accessed 2019 4, June.
47. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67:48.
48. Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. *BMJ*. 2001;323:1123–1124.
49. O'Connell NS, Dai L, Jiang Y, Speiser JL, Ward R, Wei W, Carroll R, Gebregziabher M. Methods for analysis of pre-post data in clinical research: a comparison of five common methods. *J Biom Biostat*. 2017;8:1–8.
50. Brook RD, Rajagopalan S. "Stressed" about air pollution: time for personal action. *Circulation*. 2017;136:628–631.
51. Baumgartner J, Carter E, Schauer JJ, Ezzati M, Daskalopoulou SS, Valois MF, Shan M, Yang X. Household air pollution and measures of blood pressure, arterial stiffness and central haemodynamics. *Heart*. 2018;104:1515–1521.
52. Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, Morishita M, Marsik FJ, Kamal AS, Kaciroti N, Harkema J, Corey P, Silverman F, Gold DR, Wellenius G, Mittleman MA, Rajagopalan S, Brook JR. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. *Hypertension*. 2009;54:659–667.
53. Cosselman KE, Krishnan RM, Oron AP, Jansen K, Peretz A, Sullivan JH, Larson TV, Kaufman JD. Blood pressure response to controlled diesel exhaust exposure in human subjects. *Hypertension*. 2012;59:943–948.
54. Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, Silverman F. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation*. 2002;105:1534–1536.
55. Byrd JB, Morishita M, Bard RL, Das R, Wang L, Sun Z, Spino C, Harkema J, Dvonch JT, Rajagopalan S, Brook RD. Acute increase in blood pressure during inhalation of coarse particulate matter air pollution from an urban location. *J Am Soc Hypertens*. 2016;10:133–139.e134.
56. Lucking AJ, Lundback M, Barath SL, Mills NL, Sidhu MK, Langrish JP, Boon NA, Pourazar J, Badimon JJ, Gerlofs-Nijland ME, Cassee FR, Boman C, Donaldson K, Sandstrom T, Newby DE, Blomberg A. Particle traps prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men. *Circulation*. 2011;123:1721–1728.
57. Hunter AL, Unosson J, Bosson JA, Langrish JP, Pourazar J, Raftis JB, Miller MR, Lucking AJ, Boman C, Nystrom R, Donaldson K, Flapan AD, Shah AS, Pung L, Sadiktsis I, Masala S, Westerholm R, Sandstrom T, Blomberg A, Newby DE, Mills NL. Effect of wood smoke exposure on vascular function and thrombus formation in healthy fire fighters. *Part Fibre Toxicol*. 2014;11:62.
58. Pope CA III, Burnett RT, Krewski D, Jerrett M, Shi Y, Calle EE, Thun MJ. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation*. 2009;120:941–948.
59. Glantz SA, Parmley WW. Even a little secondhand smoke is dangerous. *JAMA*. 2001;286:462–463.
60. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke. *Circulation*. 2005;111:2684–2698.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Eligibility and Recruitment/Screening Process

Eligibility criteria were:

- 18 to 35 years old at the time of recruitment;
- never smokers;
- body mass index between 19 to 28 kg/m^2 with body weight greater than 50 kg;
- no history of heart disease, diabetes, kidney disease, systemic sclerosis, or any chronic inflammatory disease such as asthma, arthritis, or severe allergies;
- normal non-hypertensive blood pressure, normal electrocardiogram, spirometry values greater than 70% of the predicted value for the age/gender, and normal blood test results (including no evidence of iron-deficient anemia), as determined at the screening exam;
- not currently taking statins, anti-inflammatory medication, or other medications unless cleared by the study physician during the screening exam (cleared medications: oral contraceptives, some daily anti-depression/anxiety medications);
- no use of tetrahydrocannabinol or illicit drugs within the past three months;
- no ear or abdominal/thoracic surgery in the past month; no cancer (current or in remission for less than six months); no central intravenous line or port; never had a mastectomy;
- no pacemaker;
- not currently pregnant, breastfeeding, or planning a pregnancy within six months;
- not regularly exposed to smoke, dust, fumes, or solvents (occupationally or recreationally/at home), or regularly burned candles or incense within the last three months;

- no history of claustrophobia;
- no fear of needles;
- not planning to donate blood during the timeframe of participation;
- no latex allergy; and
- live within 20 miles of the study facility and not planning to move more than 20 miles away within six months.

Individuals interested in participating in the study completed a screening questionnaire to determine potential eligibility. Individuals who appeared to meet criteria based on this questionnaire were asked to attend an in-person screening exam to ensure that the participant met health-based eligibility criteria. At the screening exam, medical staff measured the individual's height, weight, and blood pressure. A physician reviewed the recruitment questionnaire with the individual, conducted a physical exam, and reviewed the individual's medical history, including family history of cardiovascular and respiratory disease. Additionally, the individual performed an electrocardiogram, spirometry test, and a blood draw for analysis of complete blood count, comprehensive metabolic panel, lipid levels, and serum ferratin. A physician reviewed all results from the screening exam to make a final determination of eligibility for the study.

Additionally, individuals received a tour of the study facility and an overview of the study process, requirements, and expectations at the time of their screening exam. The goal of the tour and overview was to familiarize potential participants with the exposure facility, protocols, and staff, to reduce drop-out rates and alleviate potential stress-related reactions to the contrived exposure experience during their participation. During the tour, study staff showed individuals examples of cookstoves such as those used for the treatments, explained how the exposure chamber worked and safety features of the chamber (e.g., non-locking doors, the intercom and messaging

system to communicate with staff, emergency shut-offs, and pollution level monitoring), and described what the participant experience was like during exposure periods and throughout the health measurements. Individuals were able to see the exposure chamber and, if not in use during the time of their screening exam, enter the exposure chamber.

Treatment Sequence Assignments

The study protocol called for each participant to receive six exposure treatments (a clean air control and five treatments of cookstove air pollution). There was a washout period between treatments that was typically two weeks but up to six weeks by design, due to holidays and other similar schedule constraints. Our study followed a modified Williams square design, which is a Latin square crossover design that is balanced across treatments and first-order carry-over effects. We specified six unique sequences of treatments. Each sequence contained all six treatments administered in a unique order across the participant's six study sessions. Across all sequence groups, each treatment appeared once in each of the six "periods" (visit numbers) of the treatment orders (e.g., first through last assigned study session) and was both followed by and preceded by each other treatment exactly once. This design controls for time-invariant personal level factors and is robust to time-variant factors that might differ from one study session to the next. Participants were blinded to their sequence.

We conducted the study in three rounds (October 2016 to February 2017; March to June 2017; August 2017 to January 2018). In each round, two sequence groups (8 participants each) completed their full set of six treatments on alternating weeks. Additionally, within each sequence group, we divided participants into two subgroups (4 participants each) who completed their session on different days of the week (Mondays or Wednesdays). For the four participants who completed their study sessions on the same day, we staggered start times by 30 minutes.

Participants who missed a scheduled study session (due to illness or unforeseen conflict) were allowed to make up the missed treatment at the end of the sequence.

Participants were scheduled each study day with 30-minute staggered start times between 7:30AM and 9AM; each participant was scheduled for the same start time for each of their six study sessions. Assignment of participants into sequence groups, week days, and time slots was random; however, we did consider each participant's availability for aspects of the randomization (i.e., participants were recruited on a rolling basis into the ongoing study round and were allowed to specify whether they were not available to be placed into certain dates/time slots). Researchers were blind to the treatment orders within each sequence during the assignment process.

Participants who missed a scheduled study session (due to illness or other unforeseen conflict) were allowed to make up the missed session at the end of the sequence. Makeups were not necessarily completed on the same day of week or starting time as their regular schedule. Makeups were conducted ten days to 14 weeks after the last scheduled treatment, scheduled based upon participant and study schedule constraints. Participants remained blind to the treatment during makeups.

Treatments and Administration

Stove makes/models were as follows:

1. Liquefied petroleum gas [LPG] stove: Classic Single Burner 25000 BTU, WokSmith, China
2. Gasifier: Ace 1 Gasifier, African Clean Energy (Pty) Ltd, Lesotho
3. Forced draft (fan-powered) rocket elbow: HomeStove, Biolite, USA
4. Natural draft rocket elbow: G3300, Envirofit International, USA
5. Traditional three stone fire: open fire, bricks in U-shape used to contain fuel

The filtered air (target $PM_{2.5}$: 0 $\mu g/m^3$) was generated by drawing conditioned laboratory air through a high-efficiency particulate air (HEPA) filter. Pollution was generated within a total-capture fume hood, diluted with HEPA-filtered laboratory air, and then drawn into the exposure chamber. A nephelometer (DustTrak DRX 8533, TSI Incorporated, USA) with a $PM_{2.5}$ size-selective cyclone inlet was calibrated to the wood and LPG stoves separately (based on gravimetric filter data). The DustTrak and a gas analyzer (Siemens Ultramat 6E, Siemens AG, Germany) were used to monitor $PM_{2.5}$, carbon monoxide (CO), and oxygen levels in the chamber in real time; humidity and temperature were also monitored (Omega HX94BC transmitter and Type K thermocouple, OMEGA Engineering, USA). A dynamic control system (LabVIEW™, v15.0 32-bit, National Instruments, USA) was used to automate the flows of both dilution of pollution air based on real-time $PM_{2.5}$ data received from the DustTrak.

While in the exposure chamber, participant were asked to remain seated at assigned desks and to avoid watching suspenseful videos, talking to each other, or talking on a cell phone for the duration of the exposure period; however, activities within the facility were not otherwise restricted (participants were allowed to use computers/internet, read books, listen to music, nap, etc.). Participants wore noise-canceling headphones while inside the exposure chamber, which reduced the noise generated by the exposure delivery system and allowed the study nurse to communicate with them from outside the chamber via intercom. We attempted to blind participants to their treatments on a given study day; however, full blinding was not feasible as higher-PM treatment levels (e.g., fan rocket, rocket elbow, three stone fire) have a distinct wood smoke smell that participants could identify when they entered the exposure chamber.

Additional characterization of stove emissions within the facility was conducted at the end of the study, at least twice per treatment type in randomized order. For each characterization test,

the facility was operated for two hours under the same conditions as during human exposures, but without participants present, on at least two occasions per treatment type. Air was sampled at breathing zone height 1 m from the wall of the facility (approximating the location where participants sat). Gravimetric $PM_{2.5}$ measurements were made by sampling air at 16.7 L/min through a $PM_{2.5}$ size-selective cyclone (URG Corporation, USA) onto polytetrafluoroethylene membrane filters (47mm, Tisch Environmental, USA), which were analyzed offline. Particle number size distributions (10 to 500 nm) were measured with a scanning mobility particle sizer (SMPS 3081-3785, TSI Inc., USA). Elemental and organic carbon concentrations were determined using thermo-optical analysis (OCEC Analyzer, Sunset Laboratory, USA) on pre-baked quartz filters (Tissuequartz, Pall Life Sciences, USA). The quartz filter samples were collected by sampling at 16.7 L/min through the $PM_{2.5}$ size-selective cyclone. Nitrogen oxide and nitrogen dioxide were measured at 1 Hz via chemiluminescence (Model 42i-TL, Thermo Scientific, USA). Gas-phase carbonyls were measured by sampling onto 2,4-dinitrophenylhydrazine silica-based cartridges downstream of an ozone scrubber (Sep-Pak, Waters, USA) and analyzed offline using high-performance liquid chromatography with ultraviolet detection. Whole air samples were collected in 2-liter electropolished stainless steel canisters equipped with Silonite-coated flow controller valves (Entech Instruments Inc., USA) and analyzed offline for volatile organic compounds using gas chromatography/mass spectrometry.

Health Measurements

A series of cardiovascular and pulmonary health measurements was taken at four time points: before exposure, immediately after exposure, 3 hours post exposure, and 24 hours post exposure. Each series of measurements took approximately one hour to complete. Measurements were taken in the same order at each time point and across each study session, as indicated below:

1. Apply Holter monitor for heart rate variability (HRV) measurement (at the baseline time point only; the Holter monitor remained in place for the first three time points only).
    2. Rest period in supine position lasting twenty minutes during time points one, two, and three (HRV data collected during last 10 minutes) and ten minutes during time point 4 (no HRV data collected).
    3. Blood pressure and pulse wave analysis (for Augmentation Index) using SphygmoCor device (participant remained in supine position; measurements conducted on left side using appropriately sized cuffs).
    4. Pulse wave velocity using SphygmoCor device (participant remained in supine position).
    5. Spirometry using Easy-on device (participant in seated position).
    6. Venous blood draw for analysis of inflammatory markers, complete blood count, and lipid levels.

Safety Considerations and Informed Consent

We received approval to conduct this study from the funding agency (NIH) and the Colorado State University Institutional Review Board. As part of this process, we provided both agencies with extensive justifications related to participant safety.

Only one of the study treatments (the traditional open fire wood stove; 500 $\mu g/m^3$) resulted in exposure levels above the US daily regulatory standard for fine particulate matter (currently 35 $\mu g/m^3$ for the 24-hour average); assuming 500 $\mu g/m^3$ exposure for 2 hours and 8 $\mu g/m^3$ for the rest of the 24 hours in a day (typical background concentration in Fort Collins, Colorado, the study location) would result in a 24-hour average of 49 $\mu g/m^3$. Using similar calculations, the rest of the study treatments result in daily exposure averages below the daily standard for particulate matter

(and below the standards for other ambient criteria pollutants). Furthermore, the US Environmental Protection Agency National Ambient Air Quality Standards are set to protect all citizens, including those who are most susceptible (e.g., children, the elderly, or those with existing cardiovascular or respiratory disease). Our study included only healthy, never-smoker adults to minimize potential risks.

We used strict eligibility criteria to ensure participants in this study were healthy and therefore, at low risk of both acute and chronic harm from exposure to the air pollution in the study. We excluded potential participants who: had a history of heart disease, diabetes, or any chronic inflammatory disease (such as asthma, arthritis, or severe allergies); body mass index (BMI) less than 19 or greater than 25; were currently pregnant or planning a pregnancy during the exposure period; regularly taking statins or other anti-inflammatory medication; occupationally exposed to dust, fumes, solvents, or secondhand smoke. All participants were examined by a board-certified cardiologist prior to enrollment to determine eligibility, including a full medical history and routine physical exam, EKG, spirometry, and bloodwork. Normal EKG, spirometry, and blood work were prerequisites for entry into the study. Participants were instructed to tell study staff if they had any change in health during their participation in the study, so that we could reassess eligibility.

The exposure chamber facility was monitored in real-time by trained staff to ensure $PM_{2.5}$ concentrations were maintained within reasonable ranges of the target, planned concentrations and that CO, oxygen, temperature, and humidity remained within acceptable levels. The facility was equipped with an alarm that would trigger if the PM concentration delivered to the chamber exceeds 600 $\mu g/m^3$ across a 2-min average, at which point the cookstove exhaust would automatically shut off and subjects were to be instructed to leave the chamber immediately (this

did not ever occur). Participants were informed of additional safety features, including non-locking doors that could easily be pushed open at any time, windows through which they could see study staff (and were being watched by study staff, including a registered nurse, at all times), monitoring of blood pressure and pulse oxygen every 15 minutes, and various methods for communicating with staff who were outside the facility. A physician and registered nurse were present during the controlled exposure periods; the physician remained on-call for 24 hours after the end of the exposure period.

The informed consent document contained a description of each of the exposures, comparing the level to easy-to-understand references (e.g., for 250 $\mu g/m^3$ $PM_{2.5}$, we noted that similar exposures occurred in Fort Collins during the 2012 High Park fire, a major wildfire that occurred in a nearby area). The consent form described the risks of air pollution exposures, with following statements:

- Short-term exposure to air pollution ($PM_{2.5}$), like that which will be experienced in this study, poses limited risks to young, healthy participants. Long-term (over the course of decades) exposure to air pollution may increase the chance of adverse health effects, but this study is considered short-term exposure.
- Short-term exposure to carbon monoxide (CO) has been associated with headaches, dizziness, nausea, and/or vomiting. With the exception of headaches, these symptoms typically occur at concentrations higher than the maximum concentration (200 ppm) participants may experience while inside the SET facility. Participants will immediately be escorted out of the SET facility should CO concentrations in the SET facility exceed the recommended exposure limit (200 ppm) set forth by the National Institute for Occupational Safety and Health.

All participants went through the informed consent document in-person with study staff, who verbally explained the details in the written document to ensure participants understood the types of exposures and exposure levels. Participants were given the chance to ask questions.

Statistical Analysis: Confounders

Descriptive statistics were calculated and bivariate analyses were conducted to confirm that associations between these covariates and the treatment groups did not occur by chance or due to imbalances caused by missing data.

For categorical variables (e.g., yes/no consumption of alcohol; bike, car, walk, bus mode of commute), we tallied the number of individuals who reported each category by treatment type. We also tallied the number of individuals who changed their reported answer from one study period to the next. For continuous variables (e.g., ambient CO concentrations), we calculated the mean, minimum, and maximum value per treatment type. Descriptive analyses for continuous variables included determining mean, minimum, and maximum values for the variable by treatment type.

For variables that showed variation across treatments, we ran models to predict the confounder status by treatment type, to determine if there were meaningful differences in the variable by treatment type. The models predicted the outcome of the confounder status (e.g., binary alcohol, caffeine, and medication consumption status; continuous ambient conditions) with a fixed effect of categorical treatment type and a random person intercept to account for non-independence across repeated measures within our crossover design (i.e., each individual completing multiple treatments). We also ran a multivariable model that contained the treatment effect adjusted for multiple potential confounders.

Data S2.

Supplemental Results

Treatments

Summaries of the addition pollutant characterizations are provided in Table S1 and Figure S1. Gravimetric measurements and time-resolved $PM_{2.5}$ measurements made during the emissions characterization were consistent with the target concentrations for each stove on study days.

Study Completion/Missing Data

Of the 26 participants who missed study sessions, 12 missed only one session. Approximately half of the missed study sessions were due to scheduling conflicts that arose after a participant enrolled in the study; one quarter were due to illnesses on scheduled study dates, and one quarter were due to the participants being enrolled in the study late, after the rest of their sequence cohort had completed the first study session.

Four participants withdrew from the study prior to completing six study sessions. Additionally, errors with data logging and our exposure chamber operation resulted in the loss of data relevant to single sessions that were not repeated for five participants. Finally, one participant completed six study sessions, however after the first session, we switched from left-side measurements to right-side to accommodate a medical implant in their left arm; their first session was therefore censored from the dataset. More study sessions were missing from the LPG, gasifier, and fan rocket treatments (44 of the 48 participants completed these treatments) than other treatments (rocket elbow: 45, three stone fire and control: 47). Within the sessions completed, 11 individual data points are missing. Reasons for missing individual data points included scheduling

conflicts for participants that resulted in them leaving a study day without completing the three-hour or 24-hour follow-up time point or a data recording error that resulted in loss of data.

Age, sex, and BMI were comparable between participants who missed sessions and those who did not. For the 22 participants who completed all treatments within sequence, 55% were male, average BMI was 23.4 ± 2.3 kg/m^2 (range 19.4 to 28.7), and average age was 28.4 ± 4.0 years (range 20.7 to 36.1). For the 26 participants who completed all treatments within sequence, 54% were male, average BMI was 23.4 ± 2.2 kg/m^2 (range 19.4 to 27.6), and average age was 26.9 ± 3.1 years (range 21.9 to 34.1).

Health Measurement Timing

Baseline pre-exposure measurements occurred on average 25 minutes before entering the exposure facility (range 66 to 12 min). The three sets of post-treatment health measurements were scheduled to start immediately post-exposure, three hours post exposure, and 24 hours post-exposure. The average times of blood pressure measurements were 30 minutes (range: 16 to 49 min; standard deviation: 4.2 minutes), 3 hours and 26 minutes (range: 3 hours 12 min to 3 hours 47 min; standard deviation: 4.8 minutes), and 24 hours and 13 minutes (range 22 hours 13 min to 25 hours 44 min; standard deviation: 30 minutes) post-exposure. Individuals were consistent with themselves across sessions: the average difference in time of day at which each individual's health data were collected was 10 minutes, 11 minutes, and 38 minutes for immediately, three hours, and 24 hours post-exposure, respectively.

Potential Confounders

Alcohol, Caffeine, and Medication Use

Reported alcohol consumption, caffeine intake, and medication use among participants was low (see Tables S2 and S3). Univariate models did not find statistically significant associations between alcohol use, medication use, or caffeine use and treatment type (not shown).

Mode of Commute

Participants were asked to use the same mode of commute into the facility on each study day. Driving was the most common mode of commute (59% of all trips to the facility for the first study day and 56% of all trips for the second study day involved a car), followed by bike (36% of all trips on the first study day and 31% on the second study day; see Tables S4 and S5). Twenty-five of the 48 participants did not change their habits regarding first day commute mode across the six study sessions (i.e., consistently reported the exact same mode for all six sessions). Twenty-two of the 48 participants did not change their habits regarding the second day commute mode use across the six study sessions.

Sleep Quantity

Most participants reported getting an "average" amount of sleep (self-defined "average" as the typical hours of sleep per night; 74% for the night before the study session began and 75% for the night before the second study day); the amount of people reporting below-average sleep was less for the second study day than the first (19% for the night before the study session began vs. 10% for the night before the second study day; see Tables S6 and S7). Only 11 of the 48 participants did not change their habits regarding sleep prior to the start of a study session across the six study sessions (i.e., consistently reported the exact same sleep levels for all six sessions). Thirteen of the 48 participants did not change their habits regarding sleep the night before the 24-hour measurements across the six study sessions.

Ambient $PM_{2.5}$

Mean ambient $PM_{2.5}$ (measured outdoors at a monitoring site approximately 1 mile from the study facility) in the 24-hours prior to the start of a study day ranged from 4.9 $\mu g/m^3$ (control) to 9.8 $\mu g/m^3$ (fan rocket; see Table S8). Minimum recorded mean $PM_{2.5}$ was 0.9 $\mu g/m^3$ (three stone fire) and maximum recorded mean $PM_{2.5}$ was 17.6 $\mu g/m^3$ (fan rocket). Ambient $PM_{2.5}$ was higher for all treatments compared to the control except the gasifier. However, the range of ambient $PM_{2.5}$ overall was narrow. We ran a model that was the same as the main model but with an additional covariate of 24-hour average ambient $PM_{2.5}$; results were comparable to the main model (See Figure S2).

Additionally, we considered whether the rolling average for the 24 hours prior to a blood pressure measurement (e.g., the 24 hours prior to a baseline measurement, 24 hours prior to the 3-hour post-exposure measurement) was associated with that measurement. We ran a linear mixed effect model that estimated the change in systolic blood pressure (in mmHg) for an interquartile range (IQR) change in average ambient $PM_{2.5}$ 24 hours prior to the blood pressure measurement, accounting for correlation between within-person measurements of blood pressure with a random person effect, day of week and season using a random date effect, and average ambient temperature 24 hours prior to the blood pressure measurement. Ambient $PM_{2.5}$ was not meaningfully associated with blood pressure at any measurement time point (see Table S9).

Ambient CO

Mean ambient CO in the 24-hours prior to the start of a study day ranged from 0.25 (rocket elbow) to 0.35 ppm (three stone fire; see Table S10). Minimum recorded mean CO was 0.13 ppm (LPG) and maximum recorded mean CO was 0.70 ppm (three stone fire). Ambient CO was higher for the LPG and three stone fire treatments compared to the control. However, the range of ambient CO overall was determined to be narrow enough to exclude this variable in the main model. We

also considered average CO levels for the six hours prior to the start of a study day; results were similar.

Ambient Temperature

Mean temperature in the 24-hours prior to the start of a study day ranged from 6.0 °C (43 °F; three stone fire) to 15.9 °C (61°F; fan rocket). Minimum recorded mean temperature was -8.5 °C (17 °F; rocket elbow) and maximum recorded mean temperature was 24.2 °C (76 °F; rocket elbow; see Table S11). Temperature was higher for the LPG, fan rocket, and rocket elbow treatments compared to the control. However, the range of temperatures overall was determined to be narrow enough to exclude this variable in the main model.

Fully-Adjusted Model

None of the variables explored appeared to be confounders based on limited variation across the population and/or no association with the treatment type. However, we ran a multivariable model that was equivalent to our main model (containing a random person effect, random date effect, baseline blood pressure term, and categorical treatment) but additionally included variables for alcohol use, caffeine use, medication use, sleep quantity, ambient $PM_{2.5}$, and ambient temperature. For models estimating blood pressure immediately and 3-hours post-exposure, we used the value of the binary variables that was reported for the 24 hours prior to the baseline measurement; for the 24-hour post-exposure measurement, we used the value reported for the time between the 3-hour post-exposure measurement and the 24-hour post-exposure measurement. For $PM_{2.5}$, and ambient temperature, we used the rolling average for the 24 hours prior to the measurement. Results of the model indicated that none of the added variables were

significant predictors for blood pressure; further, inclusion of the variables in the model did not meaningfully change the main effect estimates for treatment type (see Figure S3).

Alternative Models

Baseline blood pressures were lowest for the fan-rocket treatment (115.0/68.2 mmHg) followed by the control (115.2/68.6 mmHg) and highest for the three stone fire (117.0/70.2 mmHg). As such, inclusion of a baseline term in the model is justified.

Model with more structured study design parameters, in sequence data only (no makeups)

We developed a mixed-effect model that considered more structured study design parameters relevant to our Williams square, such as each individual's assigned sequence group and the day of week (Monday vs. Wednesday), and only included data that was collected within the intended sequence. Results of this model for systolic pressure indicate no statistical significance ($p < 0.05$) for the various fixed effect "design" terms (day of week, sequence group, or the sequence/day interaction term) (Table S12; Figure S4). There are no differences in main effect estimates compared to the main model with all data (Table S12; Figure S4).

Main model, in sequence only (no makeups)

We ran the main model but on a data set that excluded data collected outside of the intended treatment sequence. Results of this model for systolic pressure indicate no differences in main effect estimates compared to the main model with all data (Table S12; Figure S4).

Main model, remove when exposure value outside narrow range of target

We ran the main model excluding data from study sessions where the exposure mean was outside of a narrowed range around the target value. The narrowed ranges were:

Control: less than 5 $\mu g/m^3$ (n = 45; 2 removed)

LPG: 5-15 $\mu g/m^3$ (n = 37; 7 removed)

Gasifier: 20-60 $\mu g/m^3$ (n = 40; 4 removed)

Fan rocket: 75-125 $\mu g/m^3$ (n = 44; 0 removed)

Rocket elbow: 175-300 $\mu g/m^3$ (n = 45; 0 removed)

Three stone fire: 350-600 $\mu g/m^3$ (n = 47; 0 removed)

Results indicated no considerable differences between the estimates for the treatment effects between this model and the main model (see Figure S5).

Table S1. Characterization of exposure treatments: average emissions.

	control	LPG	gasifier	fan rocket	rocket elbow	three stone fire
Number of tests	2	2	2	2	3	2
$PM_{2.5}$ (µg/m^3; gravimetric)	2	10	44	69	196	345
$PM_{2.5}$ (µg/m^3; time-resolved)	2	12	50	214	171	445
particle number, 10-500 nm* (/cm^3)	935	17,707	15,255	54,383	69,388	104,739
particle number, 10-100 nm* (/cm^3)	584	17,254	8,925	38,433	39,427	61,404
particle number, 10-30 nm* (/cm^3)	117	15,267	3,504	12,065	9,193	4,435
particle number, 10-50 nm* (/cm^3)	304	16,620	6,156	23,783	21,985	20,550
Percent of total particle number <100 nm*	62%	97%	59%	71%	57%	59%
Percent of total particle number <50 nm*	33%	94%	40%	44%	32%	20%
EC (µg/m^3)	-1†	3	29	38	94	30
OC (µg/m^3)	6	3	8	18	43	132
EC:$PM_{2.5}$ ratio	0.0	0.3	0.7	0.5	0.5	0.1
acetaldehyde (µg/m^3)	18	32	23	19	24	62
acetone (µg/m^3)	34	47	40	33	70	75
formaldehyde(µg/m^3)	10	44	15	24	28	50
hexaldehyde (µg/m^3)	3	6	4	9	10	21
propionaldehyde (µg/m^3)	31	52	34	35	46	53
all carbonyls (µg/m^3)	107	197	128	131	194	293
NO (ppb)	1	4	2	24	24	4
NO_2 (ppb)	8	10	9	9	10	12
benzene (ppbv)	1	1	6	7	19	35
toluene (ppbv)	4	3	4	5	7	14
ethylbenzene (ppbv)	0	0	0	0	1	2
xylenes‡ (ppbv)	2	1	3	3	4	5

*electrical mobility diameter
†Negative value due to small positive EC mass measured on one artifact filter
‡Sum of o-xylene and m,p-xylene

Table S2. Alcohol, caffeine, and medication intake by treatments: 24 hours before session start.

Variable	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone	Total	% of total
Total responses	47	44	44	44	45	47	271	
Consumed alcohol	1	1	1	1	3	1	8	3
Consumed caffeine	4	4	4	5	5	2	24	9
Used medications*	4	7	6	5	7	8	37	14
Exposed to smoke	0	1	0	0	1	0	2	1

*This includes some use of daily medications that were approved by the study physician, such as oral contraceptives.

Table S3. Alcohol caffeine, and medication intake by treatments: during the study session.

Variable	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone	Total[†]	% of total
Total responses	46	44	42	43	43	47	266	
Consumed alcohol	2	1	0	0	0	0	3	1
Consumed caffeine	2	4	2	1	2	2	13	5
Used medications[*]	5	4	8	6	4	7	34	13
Exposed to smoke	0	0	1	2	0	0	3	1

*This includes some use of daily medications that were approved by the study physician, such as oral contraceptives.
[†]Total is lower than in table S2 because some participants missed the 24-hour follow-up period.

Table S4. Mode of commute to facility by treatments: before session start.

Mode	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone	Total
Bike	15	16	17	16	18	14	96
Bike+walk	0	1	1	0	1	0	3
Bus	0	0	0	0	0	0	0
Bus+walk	0	0	1	0	1	0	2
Car	27	24	23	25	24	29	153
Car+walk	3	1	1	1	0	2	8
Walk	2	2	1	1	1	1	8
Not applicable*	0	0	0	1	0	1	2
total	47	44	44	44	45	47	271

*Not applicable: The participant did not report.

Table S5. Mode of commute to facility by treatments: prior to the 24-hour health measurements.

Mode	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone	Total
Bike	14	15	12	14	14	12	81
Bike+walk	0	0	1	0	1	1	3
Bus	1	1	0	2	0	0	4
Bus+walk	2	2	3	2	3	4	16
Car	26	23	24	23	21	29	147
Car+walk	2	1	1	0	2	0	6
Walk	1	1	0	1	2	1	6
Not applicable*	1	1	3	2	2	0	9
Total	47	44	44	44	45	47	271

*Not applicable: The participant did not report or the participant was not present for the 24-hour measurements.

Table S6. Sleep quantity by treatment: night prior to start of study session.

Sleep	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone	Total
Above average	4	2	4	0	5	4	19
Average	33	36	32	36	32	32	201
Below average	10	6	8	8	8	11	51
Total	47	44	44	44	45	47	271

Table S7. Sleep quality by treatment: night prior to the 24-hour health measurements.

Sleep	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone	Total
Above average	6	7	6	8	6	7	40
Average	35	34	33	31	32	35	200
Below average	5	3	3	4	6	5	26
Not applicable*	1	0	2	1	1	0	5
Total	47	44	44	44	45	47	271

*Not applicable: Participant missed the 24-hour follow-up period/survey.

Table S8. Ambient $PM_{2.5}$ Levels* by Treatment: 24 Hours before Session Start.

$PM_{2.5}$	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone
mean	4.9	7.2	5.3	9.8	6.4	6.6
min	1.5	2.9	1.0	2.0	2.6	0.9
max	9.8	18.8	11.2	17.6	10.6	12.7

*24-hour average in $\mu g/m^3$

Table S9. Change in systolic pressure per interquartile range change in ambient $PM_{2.5}$.

Measurement time point	IQR 24-hour average ambient $PM_{2.5}$	Change in systolic pressure (mmHg) Estimate (95% CI)
Baseline	4.4	-0.10 (-0.96, 0.75)
Immediately post-exposure	4.5	-0.15 (-1.07, 0.76)
Three hours post-exposure	4.7	-0.45 (-1.42, 0.51)
24 hours post-exposure	5.6	-0.34 (-1.44, 0.76)

Table S10. Ambient CO levels* by treatment: 24 hours before session start.

CO	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone
mean	0.27	0.31	0.28	0.29	0.25	0.35
min	0.16	0.13	0.19	0.17	0.17	0.17
max	0.46	0.48	0.45	0.50	0.44	0.70

*24-hour average in ppm

Table S11. Mean temperature* (°C) by treatment: 24 hours before study session.

Temp	Control	LPG	Gasifier	Fan rocket	Rocket elbow	Three stone
mean	7.0	10.9	8.2	15.9	13.3	6.0
min	-7.3	2.9	0.5	4.6	-8.5	-3.1
max	20.2	23.9	14.0	22.3	24.2	15.3

*24-hour average in °C

Table S12. Comparison of model results for three model options: effect estimates and 95% confidence intervals for all model parameters. For random variables, value is the variance and standard deviation.

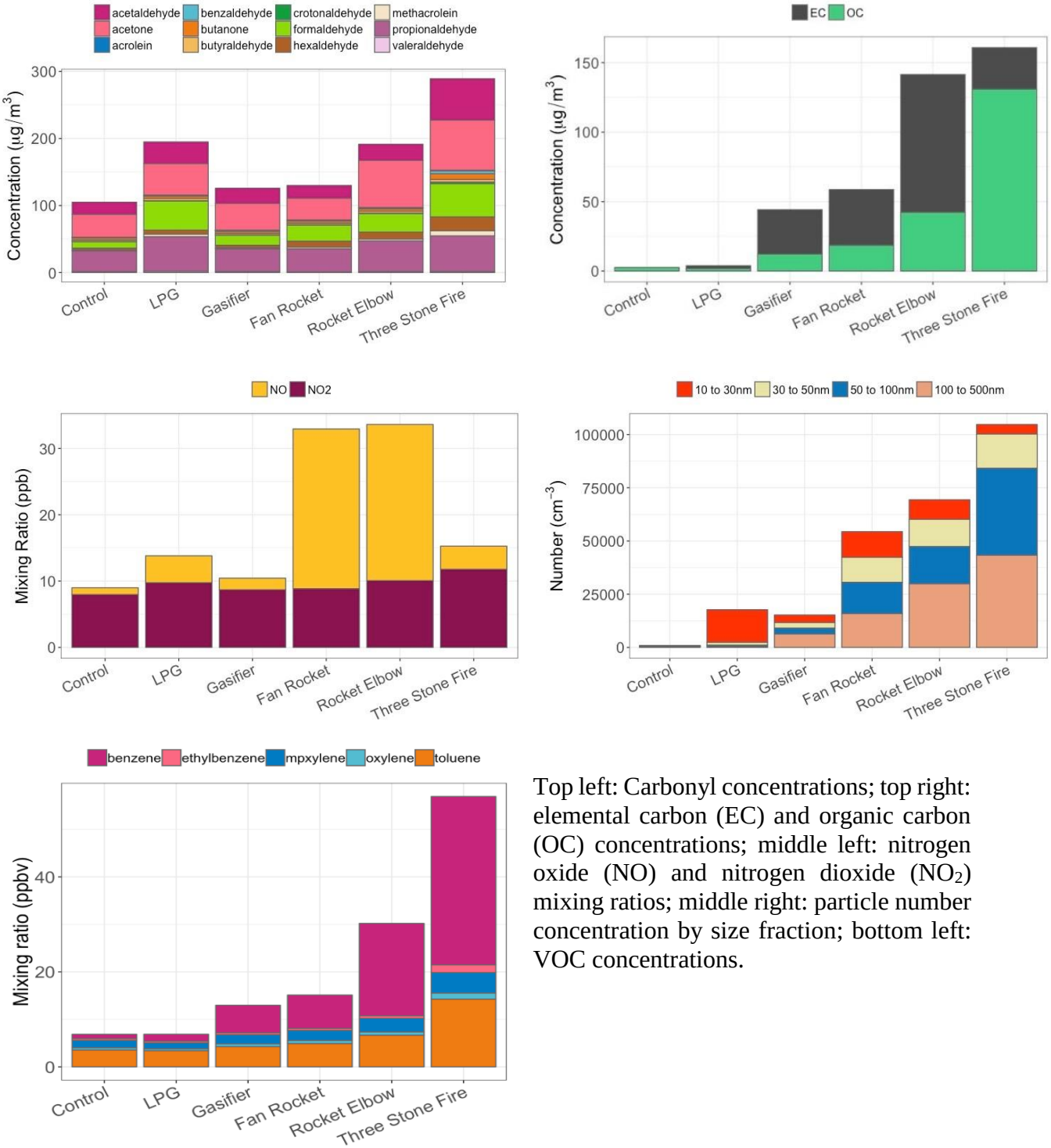
Parameter	MAIN MODEL			MAIN MODEL, IN SEQUENCE DATA			DESIGN MODEL, IN SEQUENCE DATA		
SYSTOLIC PRESSURE									
	immediately post exposure	**3 hours post exposure**	**24 hours post exposure**	**immediately post exposure**	**3 hours post exposure**	**24 hours post exposure**	**immediately post exposure**	**3 hours post exposure**	**24 hours post exposure**
n	271	267	264	243	240	240	243	240	240
random date	0.5 (0.7)	0.04 (0.2)	0.0 (0.0)	0.65 (0.8)	0.24 (0.5)	0.0 (0.0)	0.8 (0.9)	0.4 (0.6)	0.0 (0.0)
random person*	26.6 (5.2)	32.6 (5.7)	50.2 (7.1)	29.3 (5.4)	30.8 (5.5)	53.9 (7.3)	32.3 (5.7)	34.9 (5.9)	52.3 (7.3)
random residual	27.3 (5.2)	28.9 (5.4)	26.6 (5.2)	21.9 (4.7)	29.8 (5.5)	22.9 (4.8)	21.2 (4.6)	28.4 (5.3)	22.4 (4.7)
intercept	62.5 (50, 75)	71.5 (58.5, 84.6)	83.1 (69.5, 96.7)	65.3 (53.1, 77.6)	69.7 (56.1, 83.4)	87.8 (74.3, 101.2)	74.1 (60.1, 88.2)	84.1 (68.4, 99.7)	96.0 (80.5, 111.3)
Baseline BP	0.5 (0.4, 0.6)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)	0.4 (0.28, 0.51)	0.2 (0.1, 0.3)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)
LPG	-0.2 (-2.5, 2.0)	1.1 (-1.1, 3.3)	3.1 (1.0, 5.3)	0.0 (-2.1, 2.2)	1.6 (-0.8, 4.1)	2.4 (0.3, 4.6)	0.0 (-2.2, 2.2)	1.6 (-0.8, 4.1)	2.3 (0.2, 4.5)
gasifier	-1.81 (-4.0, 0.4)	1.0 (-1.2, 3.2)	2.3 (0.1, 4.5)	-1.0 (-3.3, 1.3)	1 (-1.61, 3.61)	2.2 (-0.1, 4.5)	-1.0 (-3.3, 1.3)	0.95 (-1.6, 3.5)	2.1 (-0.2, 4.4)
fan rocket	-0.4 (-2.7, 1.8)	-1.8 (-4.0, 0.5)	2.5 (0.4, 4.7)	-0.5 (-2.7, 1.7)	-1.35 (-3.9, 1.19)	2.0 (-0.2, 4.2)	-0.6 (-2.8, 1.6)	-1.5 (-4.1, 1.0)	1.9 (-0.3, 4.1)
rocket elbow	-0.6 (-2.8, 1.6)	-0.5 (-2.7, 1.7)	-0.1 (-2.2, 2.1)	-1.3 (-3.5, 0.9)	-0.31 (-2.78, 2.17)	-0.2 (-2.4, 1.9)	-1.3 (-3.4, 0.9)	-0.3 (-2.7, 2.2)	-0.3 (-2.4, 1.9)
three stone	-2.3 (-4.5, -0.1)	-2.1 (-4.3, 0.2)	2.4 (0.3, 4.5)	-1.7 (-3.8, 0.5)	-1.7 (-4.1, 0.7)	2.6 (0.4, 4.7)	-1.6 (-3.7, 0.5)	-1.5 (-3.9, 0.9)	2.6 (0.5, 4.7)
day							-0.0 (-8.6, 8.5)	0 (-9.0, 9.0)	3.4 (-7.2, 14.0)
sequence b							6.4 (-2.1, 14.9)	4.4 (-4.6, 13.3)	8.4 (-2.1, 19.0)
sequence c							-1.8 (-10.2, 6.7)	-4.5 (-13.3, 4.3)	-3.9 (-14.3, 6.6)
sequence d							-1.9	-1.2	0.1

							(-10.3, 6.5)	(-10.0, 7.7)	(-10.3, 10.6)
sequence e							-3.5 (-12.0, 5.0)	-6.8 (-15.7, 2.1)	-2.1 (-12.6, 8.4)
sequence f							-1.4 (-9.9, 7.0)	-4.5 (-13.4, 4.4)	-5.6 (-16.1, 4.9)
day: sequence b							-10.2 (-22.4, 2.0)	-12.0 (-24.9, 0.9)	-15.7 (-30.7, -0.6)
day: sequence c							1.8 (-10.2, 13.8)	4.6 (-8.0, 17.2)	2.7 (-12.2, 17.5)
day: sequence d							-4.0 (-16.2, 8.2)	-6.6 (-19.5, 6.3)	-12.9 (-27.9, 2.2)
day: sequence e							-0.2 (-12.3, 11.8)	2.0 (-10.7, 14.6)	-5.0 (-19.9, 9.8)
day: sequence f							-4.1 (-16.2, 8.0)	-2.5 (-15.2, 10.2)	-3.6 (-18.5, 11.3)
DIASTOLIC PRESSURE									
random date	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
random person*	10.8 (3.3)	12.3 (3.5)	16.7 (4.1)	11.6 (3.4)	11.6 (3.4)	16.6 (4.1)	8.6 (2.9)	10.9 (3.3)	15.9 (4.0)
random residual	13.0 (3.6)	17.4 (4.2)	20.2 (4.5)	12.5 (3.5)	17.8 (4.2)	16.9 (4.0)	12.7 (3.6)	17.8 (4.2)	15.8 (4.0)
intercept	35.3 (28.4, 42.2)	33.7 (25.8, 41.6)	44.8 (36.0, 53.6)	36.7 (30.0, 44.0)	33.6 (25.4, 41.9)	46.2 (37.8, 54.6)	38.1 (30.1, 46.1)	35.6 (26.2, 45.0)	50.0 (40.0, 60)
Baseline BP	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.4 (0.2, 0.5)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.3 (0.2, 0.5)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.3 (0.2, 0.4)
LPG	-0.7 (-2.2, 0.8)	-0.0 (-1.7, 1.7)	0.3 (-1.6, 2.2)	-0.4 (-2.0, 1.2)	0.0 (-1.9, 1.9)	-0.6 (-2.4, 1.2)	-0.5 (-2.1, 1.1)	0.02 (-1.9, 1.9)	-0.8 (-2.6, 1.0)
gasifier	-0.8 (-2.2, 0.74)	0.3 (-1.5, 2.0)	-0.4 (-2.3, 1.5)	-0.5 (-2.2, 1.2)	-0.4 (-2.4, 1.6)	-0.8 (-2.7, 1.2)	-0.6 (-2.2, 1.1)	-0.4 (-2.4, 1.6)	-0.8 (-2.7, 1.1)
fan rocket	-0.13 (-1.63, 1.4)	-0.41 (-2.2, 1.3)	-0.1 (-1.9, 1.8)	0.1 (-1.5, 1.7)	-0.4 (-2.3, 1.5)	-1.2 (-3.0, 0.7)	0 (-1.6, 1.6)	-0.5 (-2.4, 1.5)	-1.3 (-3.2, 0.5)
rocket elbow	0.4 (-1.1, 1.8)	0.2 (-1.5, 1.9)	-1.7 (-3.6, 0.2)	0.1 (-1.5, 1.7)	0.1 (-1.9, 2.0)	-2 (-3.8, -0.2)	0.1 (-1.5, 1.7)	0.2 (-1.7, 2.1)	-2.0 (-3.8, -0.2)
three stone	-0.9 (-2.3, 0.6)	-0.8 (-2.5, 0.9)	0.8 (-1.0, 2.7)	-0.7 (-2.3, 0.9)	-0.9 (-2.8, 1.0)	0.5 (-1.3, 2.3)	-0.7 (-2.3, 0.8)	-0.9 (-2.7, 1.0)	0.5 (-1.2, 2.3)
day							-1.5 (-6.2, 3.2)	-0.5 (-5.9, 4.9)	1.2 (-4.9, 7.3)

sequence b							2.1 (-2.6, 6.7)	1.0 (-4.3, 6.2)	4.2 (-1.9, 10.3)
sequence c							-2.9 (-7.5, 1.7)	-3.2 (-8.5, 2.1)	-3.3 (-9.3, 2.7)
sequence d							-4.1 (-8.8, 0.47)	-0.4 (-5.6, 4.9)	-0.8 (-6.8, 5.2)
sequence e							-2.9 (-7.6, 1.7)	-4.0 (-9.3, 1.3)	-0.9 (-6.9, 5.1)
sequence f							-3.5 (-8.2, 1.1)	-1.9 (-7.2, 3.3)	-1.6 (-7.7, 4.4)
day: sequence b							-3.9 (-10.5, 2.7)	-2.4 (-9.9, 5.0)	-7.3 (-15.9, 1.3)
day: sequence c							2.0 (-4.5, 8.6)	4.2 (-3.3, 11.7)	1.4 (-7.1, 10.0)
day: sequence d							1.7 (-5.0, 8.3)	-2.9 (-10.5, 4.7)	-7.7 (-16.3, 0.9)
day: sequence e							-2.4 (-9.0, 4.2)	-1.3 (-8.9, 6.2)	-3.2 (-11.7, 5.4)
day: sequence f							0.34 (-6.3, 6.9)	-0.9 (-8.4, 6.7)	-2.3 (-10.9, 6.2)

*In the main model and main model using in-sequence data only, variable is a random person effect. In the design model, the variable is a random person effect nested within the day and sequence group.

Figure S1. Pollutant characterization in exposure facility, by treatment.



Top left: Carbonyl concentrations; top right: elemental carbon (EC) and organic carbon (OC) concentrations; middle left: nitrogen oxide (NO) and nitrogen dioxide (NO_2) mixing ratios; middle right: particle number concentration by size fraction; bottom left: VOC concentrations.

Figure S2. Effect estimates and 95% confidence intervals for mean difference in systolic pressure (mmHg) for stove treatments compared to control for main model compared to the model including ambient $PM_{2.5}$ variable.

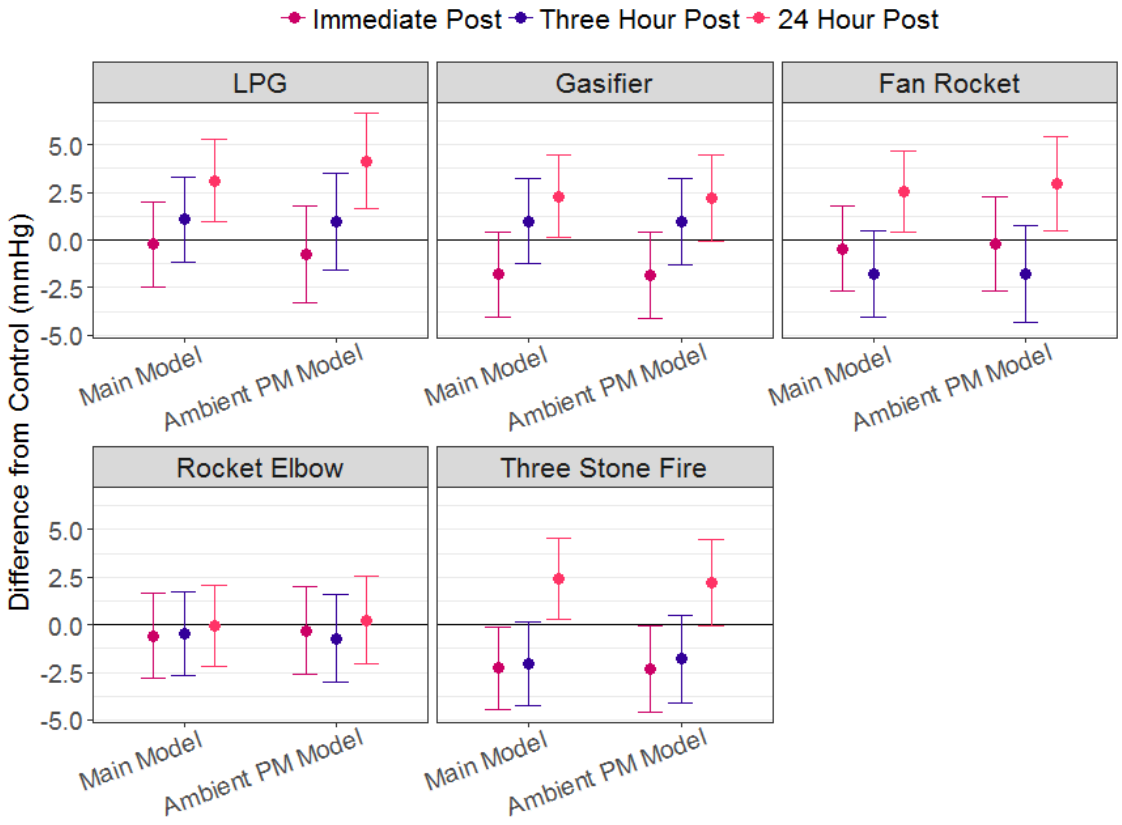


Figure S3. Effect estimates and 95% confidence intervals for mean difference in systolic pressure (mmHg) for stove treatments compared to control for the main model versus the fully adjusted model. Fully adjusted model contains additional variables of alcohol consumption, caffeine consumption, medication use, sleep quantity, ambient $PM_{2.5}$, and ambient temperature.

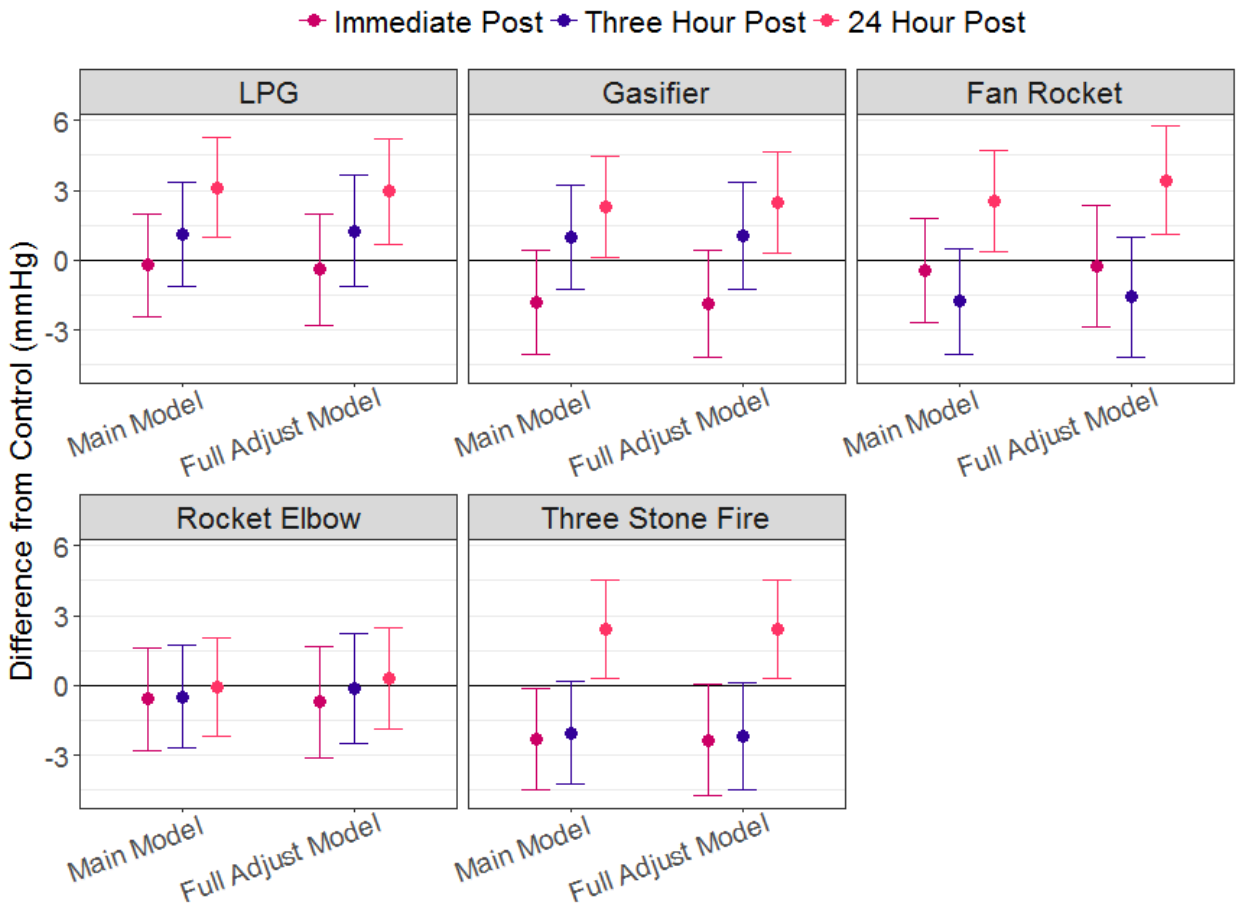


Figure S4. Effect estimates and 95% confidence intervals for mean difference in systolic pressure (mmHg) for stove treatments compared to control for the three model types.

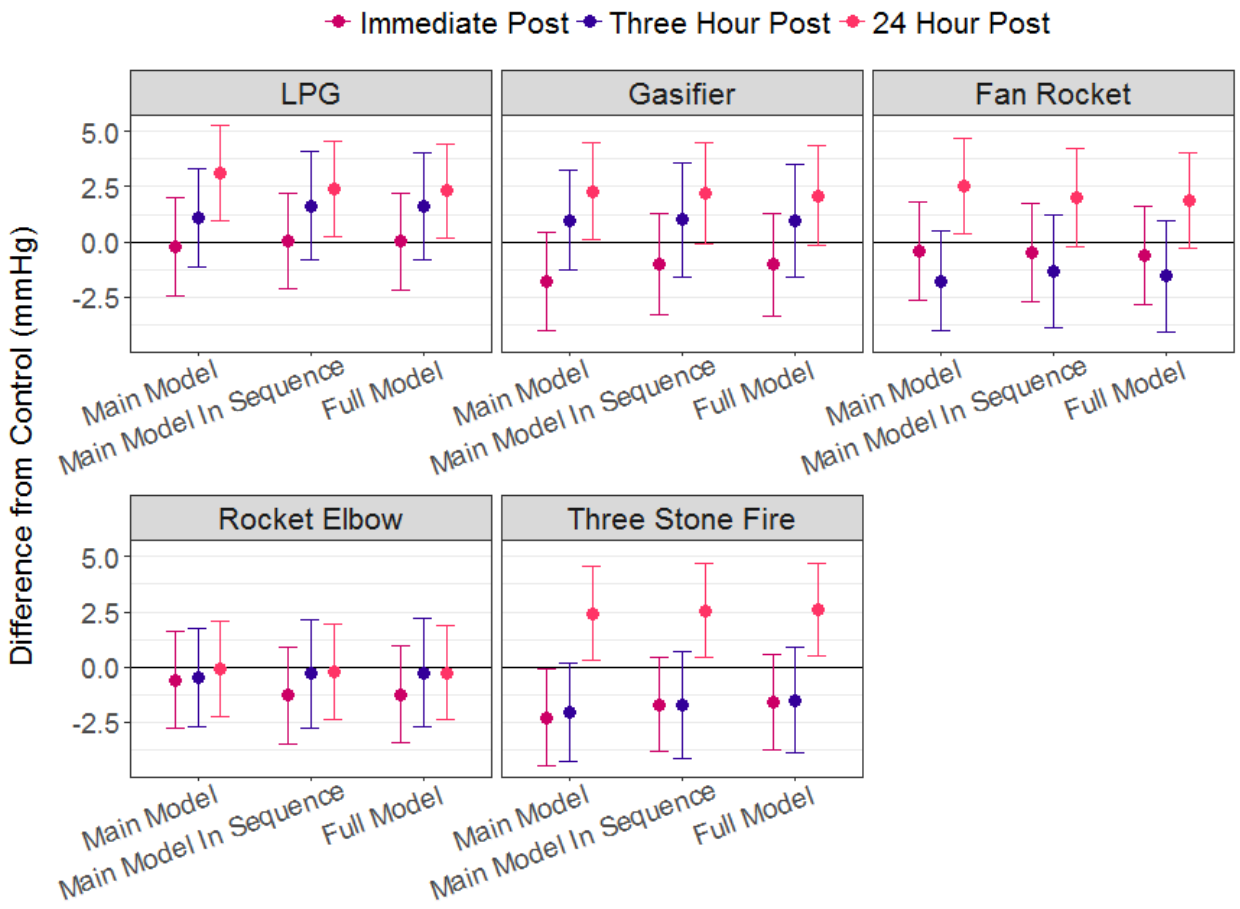


Figure S5. Effect estimates and 95% confidence intervals for mean difference in systolic pressure (mmHg) for stove treatments compared to control: comparison of main model to model with exposure outliers removed.